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THE DIFFERENTIAL DIAGNOSIS OF INTESTINAL MALABSORPTION WITH I^{131}-FAT AND FATTY ACID *†

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THE absorption of fat from the intestinal tract is a poorly understood body process. The lack of understanding is the result of having available only cumbersome and inaccurate conventional methods with which to study fat absorption. Certain large gaps which exist in our knowledge of the intermediary metabolism of lipids also contribute to this situation. The availability of isotopically labeled fat provides a new, simplified and more specific tool for the study of fat absorption. One of us (D. A. T.) has developed a method for the preparation and use of I^{131}-labeled fat in the study of the absorption, utilization and deposition of fat in both dog and man.[1] The present report is concerned with the use of that method as a routine clinical procedure in the differential diagnosis of steatorrhea.

METHODS

The I^{131}-fat as triolein or oleic acid ‡ was formerly made in this laboratory, and it is probable that the unsaturated fat was labeled at the C-9 double bond. $I^{131}C1$ was used in the labeling procedure so that a stable chlorine atom and a radioiodine atom saturated the oleic acid molecule at adjacent positions (C-9, C-10).

* From the Symposium on Diseases of Intestinal Absorption, presented (in part) at the Thirty-eighth Annual Session of The American College of Physicians, Boston, Massachusetts, April 9, 1957.

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‡ Now available from Abbott Laboratories.

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Fifty microcuries of the I^{131}-fat activity were administered to the fasting patient in 30 gm. of olive oil as carrier. Thyroid uptake of any free I^{131} was reduced by the prior administration of iodide. A fat-free breakfast was given after the labeled meal to stimulate normal gastric and intestinal emptying and peristalsis. Blood specimens were taken at two, three, five, six and eight hours. A fasting sample of blood was used as the base line reference.

The serum was precipitated with 40% trichloracetic acid and washed with 10% KI until no traces of activity remained in the supernatant. The I^{131}-lipid activity was measured by counting the samples in a Nuclear-Chicago DS-3 scintillation well-counter. The results were expressed as lipid activity

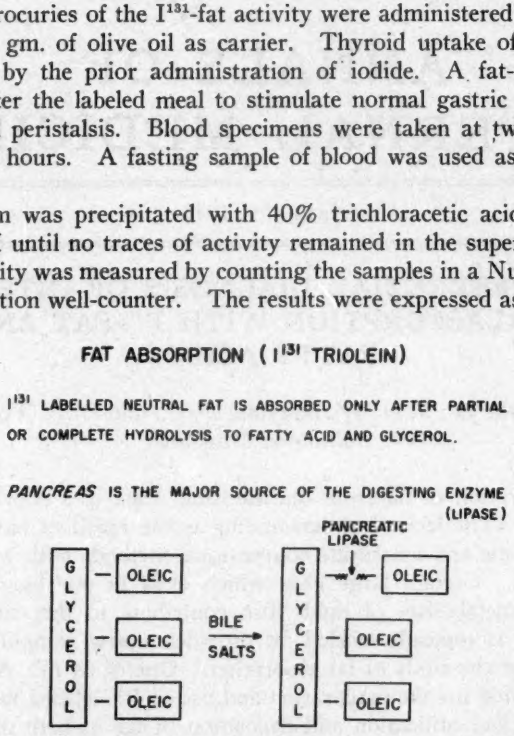

FIG. 1. Absorption of neutral fat.

per cent of the administered dose per calculated total blood volume. Serum turbidity was determined by reading each serum sample in a Coleman Jr. spectrophotometer at a setting of 650 μ. Patients with a variety of proved pancreatic and intestinal abnormalities were studied with one or both tests.

RESULTS

Our initial studies concentrated on the use of I^{131}-labeled fat as a measure of pancreatic insufficiency. I^{131}-triolein is a neutral fat (figure 1) which requires pancreatic lipase for its hydrolysis prior to absorption. In the absence or deficiency of pancreatic lipase, the neutral fat is not absorbed to any significant degree and there is an increased concentration excreted in the stool. The labeled oleic acid, on the other hand, does not require further lipolysis prior to absorption. This is the basis (figure 2) for the use of tagged neutral fat and fatty acid in the diagnosis of pancreatic insufficiency.

In patients with chronic pancreatitis (figure 3) or cancer of the pancreas (figure 4), a flat triolein tolerance curve is obtained and a significant, albeit

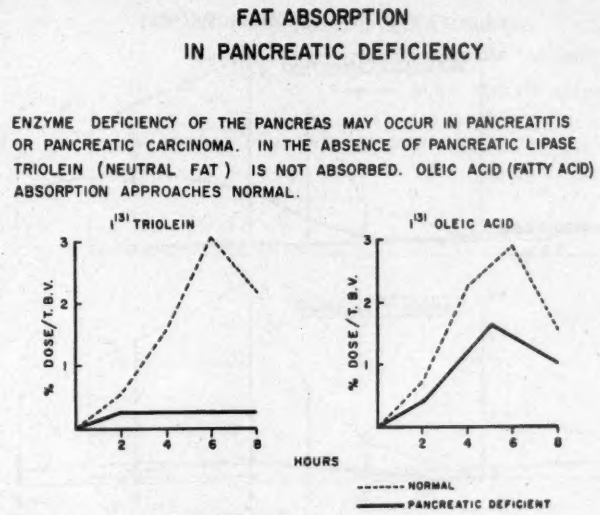

FIG. 2. Fat absorption in pancreatic deficiency.

impaired, absorption of the I^{131}-fatty acid is observed. The deficiency of I^{131}-oleic acid absorption may be partially explained by the administration of the tagged meal in olive oil. The use of I^{131}-fat and fatty acid does not differentiate chronic pancreatitis from pancreatic cancer as the cause of the

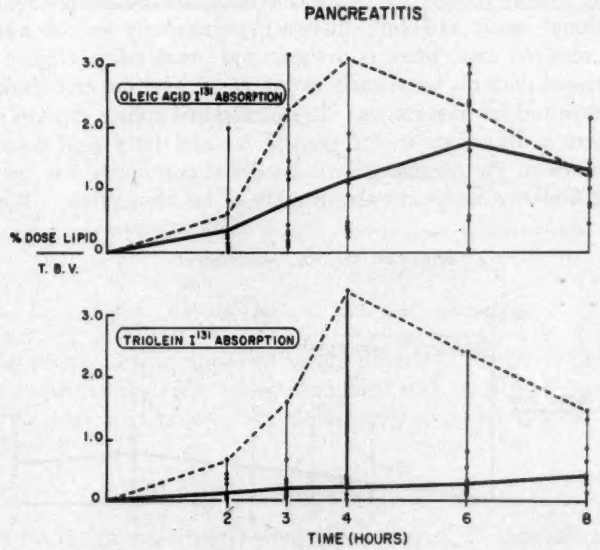

FIG. 3. Fat absorption in chronic pancreatitis. Normal - - - - - -.

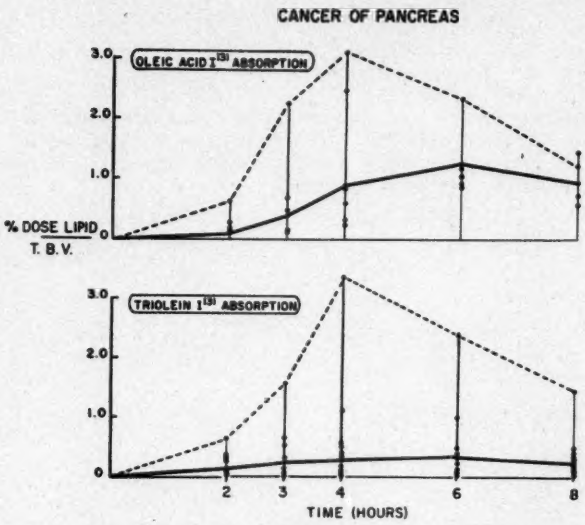

FIG. 4. Fat absorption in pancreatic cancer. Normal ------.

pancreatic insufficiency. The main value of the test is to elicit information on the specific absence of pancreatic lipase in patients with unexplained gastrointestinal malfunction and "pancreatic" steatorrhea. Definite diagnosis would usually require surgical exploration and pathologic examination.

In regional ileitis (Crohn's disease), particularly in the advanced or surgically resected case, there is a significant steatorrhea (figure 5). We have additional data on some early active cases who did not show any evidence of impaired fat absorption. In no case of Crohn's disease studied by us was there a difference in the neutral fat and fatty acid tolerance. In patients in whom the normal gastric-duodenal continuity has been altered, we did not find any consistent abnormality of fat absorption. We have not

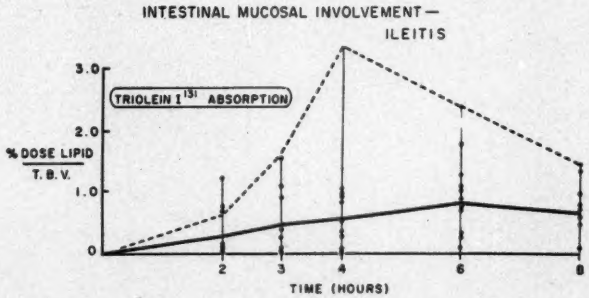

FIG. 5. Neutral fat absorption in regional ileitis. Normal ------.

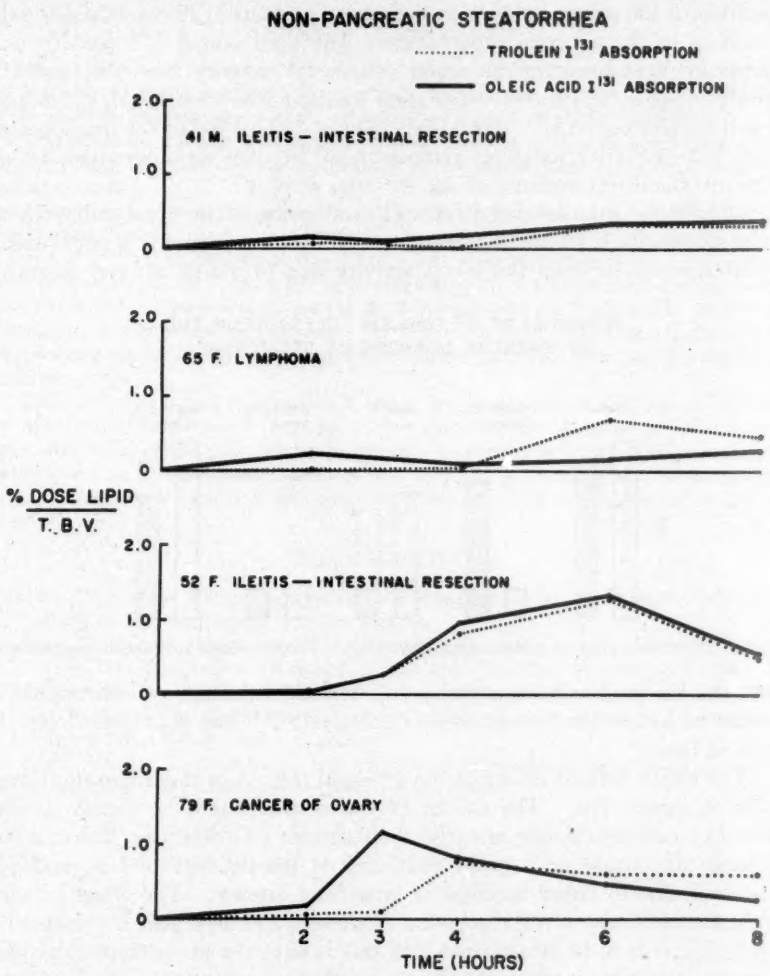

FIG. 6. Fat absorption in "intestinal" steatorrhea.

studied fat absorption in sprue or celiac disease. Figure 6 illustrates the degree of impairment of fat absorption which may be present, and the similarity of the oleic and triolein curves in selected patients with "intestinal" steatorrhea.

DISCUSSION

Stanley and Thannhauser [2] first administered I^{131}-labeled olive oil to humans and separated the I^{131}-iodide from lipid bound I^{131} by the co-pre-

cipitation of the serum lipids with the serum proteins. The iodide was said to remain in the aqueous supernatant. The lipid bound I^{131} activity was determined by subtracting the water soluble I^{131} activity from the total I^{131} activity. When this method was used by us it was found that I^{131}-iodide, as well as lipid bound I^{131}, was co-precipitated. This led to the development of the use of carrier iodide to remove the I^{131}-iodide contamination, which permitted the direct measure of the I^{131}-lipid activity.[1]

Shingleton [3] fed a labeled meal orally and measured the total radioactivity of the blood with a scintillation counter. With this method it is not possible to differentiate between the blood activity due to iodide activity liberated

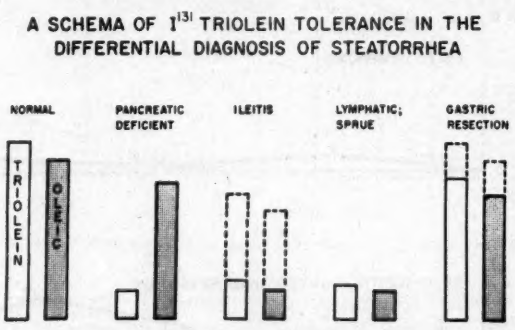

FIG. 7. Fat tolerance in malabsorption syndrome. Broken lines to indicate variations.

from the fat meal and the activity still bound to the fat. Confirmation of the use of iodide for the removal of inorganic I^{131} has also come from the work of Beres.[4]

The major clinical utility of the I^{131}-lipid tests is in the differential diagnosis of steatorrhea. The causes of steatorrhea might be simply divided into: (1) *mechanical,* due to surgical alteration; (2) *digestive,* due to a lack of pancreatic lipase or a gross deficiency in the delivery of bile, and (3) *intestinal,* due to either mucosal or lymphatic disease. The effect of some of these conditions on the absorption of triolein and oleic acid is presented in figure 7. It is to be emphasized that this is basically an attempt to provide a practical test to separate pancreatic insufficiency from the other causes of fat malabsorption. The possibility that steatorrhea might have multiple causes in an individual patient is appreciated.

SUMMARY

1. A procedure is described for the evaluation of fat absorption in the human by means of I^{131}-labeled lipid.

2. The use of tagged neutral fat (I^{131}-triolein) and fatty acid (I^{131}-oleic acid) is of value in the specific diagnosis of intestinal malabsorption due to pancreatic insufficiency.

Summario in Interlingua

In le absentia de sensibile e specific tests laboratorial pro insufficientia pancreatic, le clinico se ha vidite fortiate a diagnosticar insufficientia pancreatic predominantemente super le base de signos clinic de avantiate formas de morbo pancreatic.

Le autores ha utilisate tests de tolerantia de trioleina a I^{131} e de acido oleic a I^{131} pro differentiar le steatorrhea de insufficientia pancreatic ab steatorrhea como resultato de altere causas.

Le steatorrhea de morbo pancreatic es effectuate per un reduction o per le absentia de activitate lipolytic in le canal intestinal. In casos de iste genere, le absorption de trioleina a I^{131} es marcatemente diminuite. Isto se manifestava in un curva pauco elevate del tolerantia de lipido a I^{131} in le sanguine e in un elevation del contento fecal de lipido a I^{131}. Pauco elevate curvas de tolerantia con basse activitate de I^{131} in le sanguine e augmentos del activitate de I^{131} in le feces esseva etiam trovate in patientes con sprue, ileitis, le syndrome de vacuage gastric, e post massive resection intestinal.

Tests del tolerantia pro trioleina a I^{131} e pro acido oleic a I^{131} esseva utilisate pro differentiar inter steatorrhea de origine pancreatic e steatorrhea causate per anormalitates intestinal. In morbo pancreatic (pancreatitis, cancere del pancreas), le absorption de trioleina es reducite, sed le absorption de acido oleic es relativemente normal. In casos de anormalitate mucosal o mechanic, le absorption de ambes es defective.

BIBLIOGRAPHY

1. Turner, D. A.: The absorption, transport and deposition of fat, Ph.D thesis, 1956, University of Western Ontario, London, Ontario.
2. Stanley, M. M., and Thannhauser, S. J.: The absorption and disposition of orally administered I^{131}-labeled neutral fat in man, J. Lab. and Clin. Med. **34**: 1634–1639, 1949.
3. Shingleton, W. W., Wells, M. H., Baylin, G. J., Ruffin, J. M., and Sanders, A.: The use of radioactive labeled protein and fat in the evaluation of pancreatic disorders, Surgery **38**: 134–142, 1955.
4. Beres, P., Wenger, J., and Kirsner, J. B.: The use of I^{131}-triolein in the study of absorptive disorders in man, Gastroenterology **32**: 1–16, 1957.

JEJUNAL BIOPSIES IN SPRUE*

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Histologic studies of small bowel biopsies in sprue have received very little attention in spite of great interest in various absorptive phenomena. It is well known that the malabsorption syndrome may result from a variety of causes, and in recent years the recognition of such entities as intestinal lipodystrophy, regional enteritis and lymphoma has served to refine the diagnostic criteria for sprue. It may be hoped that further investigation of tissue pathology will lead to a clearer differentiation between the various causes of malabsorption and will contribute to the understanding of absorptive mechanisms.

New interest in small bowel pathology was aroused in 1954 when Paulley [1] reported on jejunal biopsies from two patients with idiopathic steatorrhea. He noted broadening and clubbing of the villi, which were markedly infiltrated with chronic inflammatory cells, mainly plasma cells and eosinophils. A third patient with steatorrhea, possibly due to celiac disease, showed jejunal thickening and inflammation of the serosa at laparotomy, but no biopsy of the intestine was made.

A review of the literature reveals considerable divergence of opinion as to the nature of pathologic changes, and even to the presence or absence of changes. Detailed discussions and numerous references can be found in articles by Bahr,[2] Thaysen [3] and Schein.[4]

Perhaps the earliest reference to the pathologic appearance of the small intestine in sprue was that of Thin [5] who, in 1890, noted inflammatory changes and destruction of the crypts of Lieberkühn of the jejunum, while even more marked changes were present in the ileum. He wrote: "It is here that most marked changes were found. The mucosa was almost entirely destroyed, being replaced by a structureless substance enclosing leukocytes and here and there the remains of a follicle."

In 1904 Faber [6] described the findings in a case of sprue where the abdominal cavity had been injected with formalin immediately after death. He reported a diffuse inflammation of the mucosa throughout the small bowel and ulceration of Peyer's patches, but no atrophy or change in shape of villi.

Beneke in 1910 described an atrophic appearance of the entire intestinal tract and a loss of intestinal villi, associated with an increase in goblet cells.

* From the Symposium on Diseases of Intestinal Absorption, presented at the Thirty-eighth Annual Session of The American College of Physicians, Boston, Massachusetts, April 9, 1957.

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Describing the same specimen, Justi [7] in 1913 noted broad, short, swollen villi containing many chronic inflammatory cells and an increase in fibrillar elements.

During his researches on sprue in Ceylon from 1912 to 1914, Bahr [2] found atrophic changes in the small intestine in five of seven autopsied cases. Of the two cases in his series not showing small bowel abnormality, one was probably due to disseminated tuberculosis, and the other showed too much autolysis to permit evaluation. An illustration of ileum in his monograph resembles to a striking degree some of the material to be presented here. In this drawing the epithelium is well preserved, and it is difficult to imagine that postmortem change could have produced the shortening and apparent lateral fusion of villi.

The autopsy findings in eight cases of sprue from Bombay were presented in detail by Mackie and Fairley in 1929.[8] They called attention to "withering of villi," and described a round cell infiltration of the villi together with degeneration of the columnar epithelium.

In 1931 Thaysen [9] published a review of the literature and his findings at autopsy in a single case of sprue where the abdominal cavity had been injected with formalin immediately after death. He found no remarkable lesions and concluded that the small bowel is normal in sprue, dismissing previous evidence to the contrary as due to postmortem artefact. He later reported similar findings in a case of nontropical sprue.

After Thaysen's monograph [3] in 1932, the belief was prevalent that the small intestine is histologically normal in sprue. In 1936 Fairley [10] published his agreement with Thaysen's belief, and stated that the "withering of villi" seen in India was not present in certain fresh material obtained in London.

In 1947 the findings in 16 cases autopsied by Koppisch were published. This work may have escaped the attention of many pathologists, since it appeared as part of an article by Suarez et al. dealing primarily with the treatment of sprue.[11] Koppisch noted shortening and blunting of the small bowel villi in half the cases, accompanied by an increase in the plasma cells of the tunica propria. He also noted atrophy of the heart, spleen, liver and tongue, as well as diminished spermatogenesis in the male. Adlersberg and Schein [12] in the same year reported the findings at autopsy in six cases of primary sprue and four cases of secondary sprue. The small intestine was examined microscopically in five of the primary cases, two of which showed bizarre villous shapes or clubbing. One of these cases was reported in detail by Schein,[4] who included an extensive review of the literature. This patient displayed, in addition to swollen villi, a marked hyaline change in the villous tips. Hernandez-Morales and Noya [13] described the gross appearance of the ileum in a case of acute sprue at laparotomy as having an edematous grayish appearance along with excessive distention. A biopsy was not made.

It remained for Paulley to confirm with the first reported sprue biopsies the pathology described by some of the earlier authors but discredited by Thaysen 22 years before. Paulley demonstrated anatomic changes in the small bowel and opened once again the possibility of a pathologic approach to the diagnosis and study of malabsorption syndromes. It is our purpose to present the pathologic findings in jejunal biopsies from six patients with sprue.

Material and Methods

Jejunal biopsies were obtained six to 10 inches from the ligament of Treitz during laparotomy for unrelated causes in six patients with the clinical features of sprue and laboratory-proved malabsorption. Five specimens were from multiparous women at the time of bilateral tubal ligation. One woman was untreated, having received transfusions to correct anemia prior to surgery but no specific therapy. The other four women had received folic acid at some time previously. The only male in the group had lymph node and jejunal biopsies performed to exclude Whipple's disease. Absorption was studied in all patients by oral tolerance tests as described by Gardner and Perez-Santiago.[14] Normal values were defined as follows:

Xylose: A five-hour urinary excretion of 4.4 gm. or more, after an oral dose of 25 gm. of D (+) xylose.

Vitamin A: A serum level of at least 75 μg. of vitamin A at five hours, and 125 μg. at seven hours after an oral dose of 300,000 units.

Butter fat: A serum optical density reading of 0.1000 or more, two, three or four hours after the ingestion of a standard meal containing 30 gm. of butter.

In addition, 24-hour fecal fat determinations were made for 12-day periods by a modification of the method of van der Kamer et al.[15] in four of the six patients. Previous studies in this laboratory have shown that the daily average fecal fat under these conditions does not exceed 5.4 gm. in normal subjects (3.8 gm. mean; standard deviation, ± 0.8 gm.).

Fifteen control biopsies were obtained from Puerto Rican subjects under similar conditions. One of these, being a particularly pertinent control, has been presented in some detail (case 7). This patient developed diarrhea and a severe megaloblastic anemia post partum but had normal absorption tests. The other controls had abdominal surgery for problems not related to intestinal absorption, such as peptic ulcer, cholecystectomy or trauma. None gave a history of chronic diarrhea or anemia.

Results

It will be seen (figures 1a, b and c; 4a, and 5a) that the normal jejunal mucosa displays slender, delicately ruffled villi which project freely toward the lumen for over half the total thickness of the mucosa. The villi contain

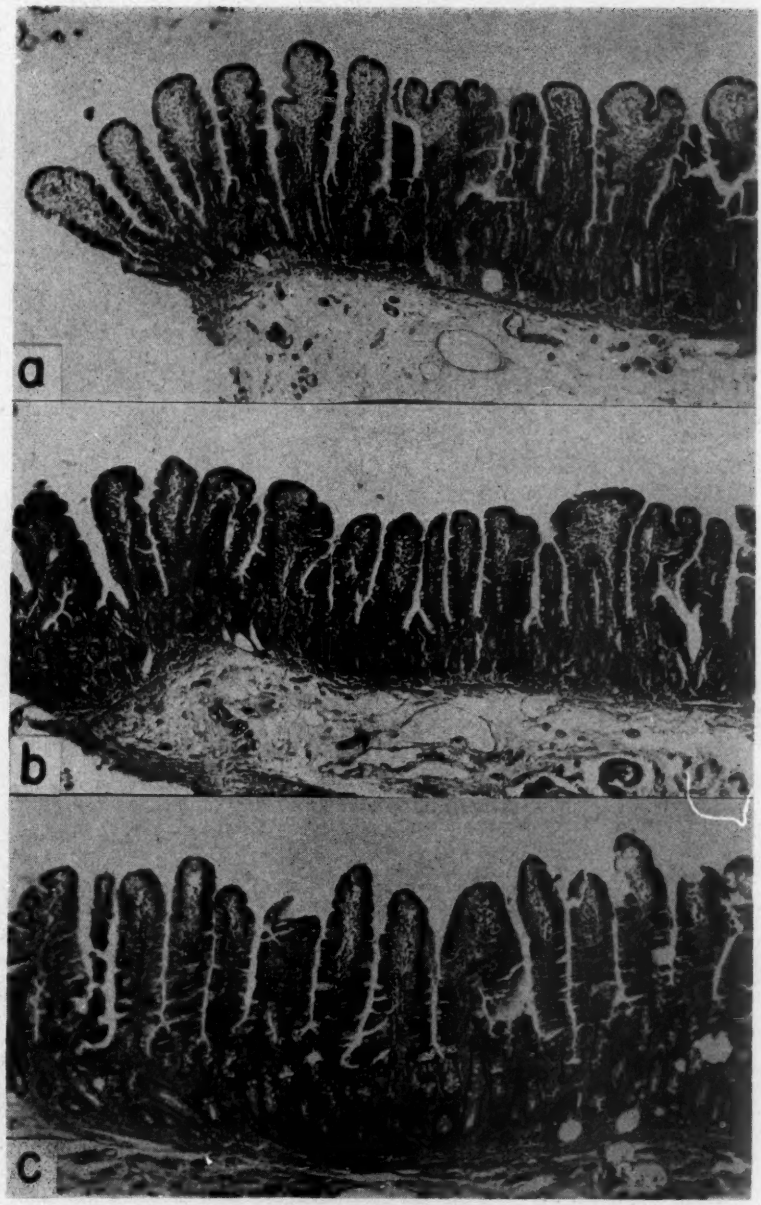

FIG. 1. A group of normal jejunal biopsies. × 35.

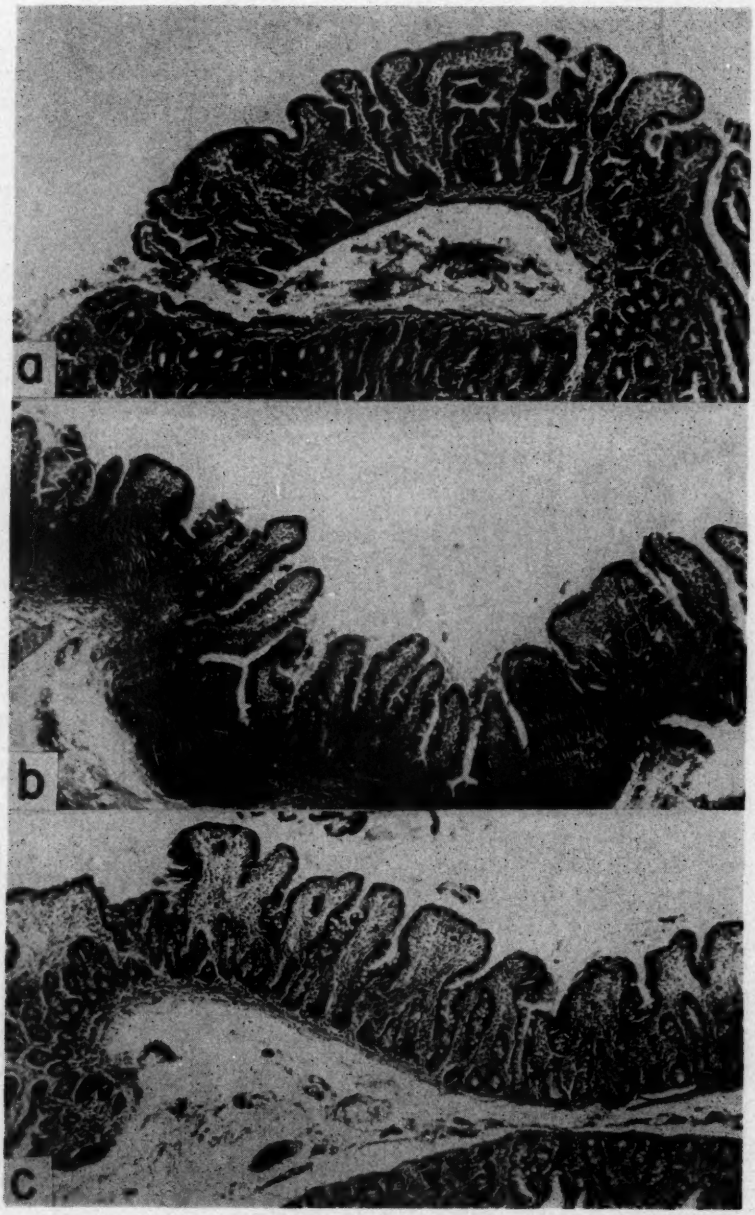

FIG. 2. Jejunal biopsies from patients with sprue, × 35. (a) Case 1; (b) case 2; (c) case 3.

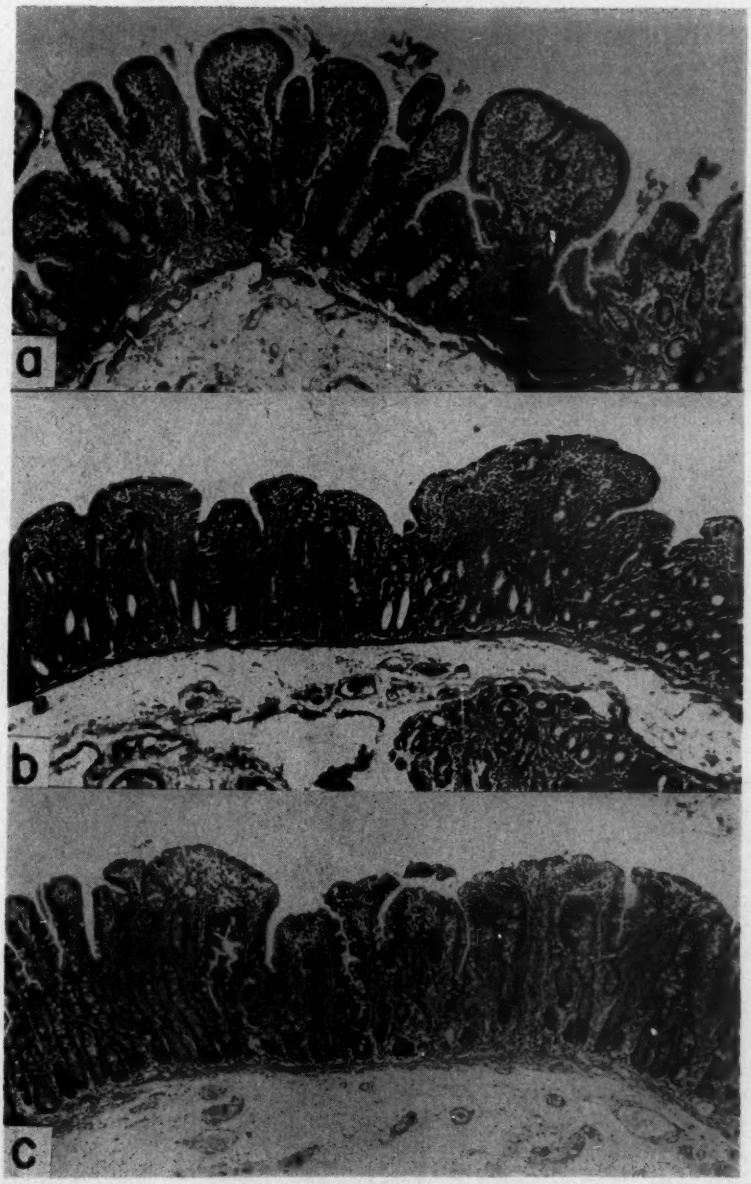

FIG. 3. Jejunal biopsies from patients with sprue. × 35. (a) Case 4; (b) case 5; (c) case 6.

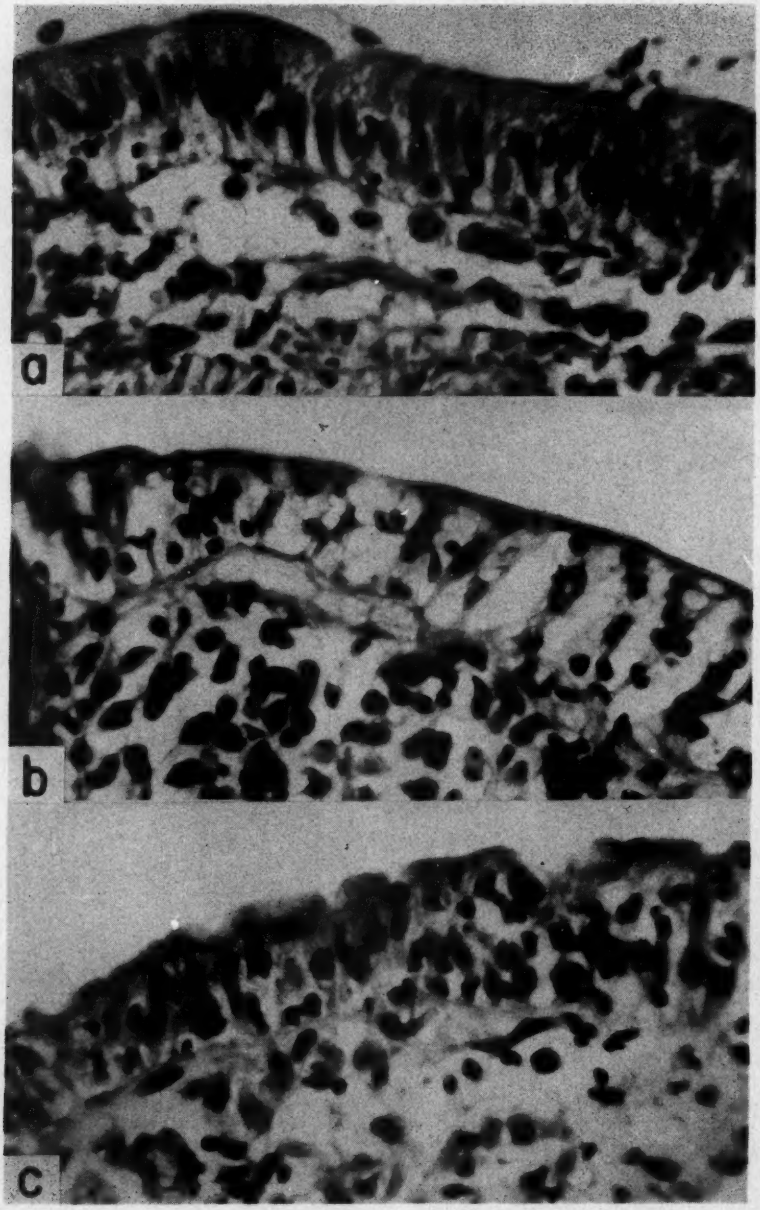

FIG. 4. The columnar epithelium. × 440. (a) normal; (b) untreated sprue, case 5; (c) treated sprue, case 6.

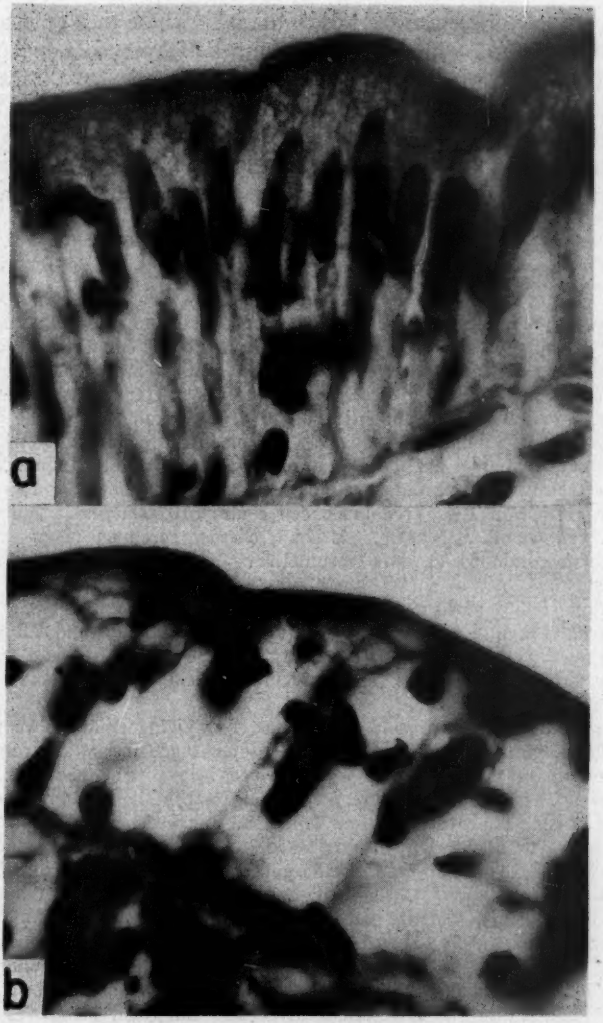

FIG. 5. Columnar epithelium. ×900. (a) normal; (b) untreated sprue, case 5.

scattered lymphocytes, eosinophils, neutrophils and plasma cells, loose fibrous supporting elements, capillaries and lymphatics. Thickened or "double" villi do not as a rule exceed one in each low power field of the microscope. The normal columnar epithelium (figure 4, top) consists of cells which in the crypts measure 30 to 40 μ in length, and toward the villus tip measure 50 to 60 μ. The nuclei measure 15 to 20 μ in length and occupy the basal

half of the cell except toward the tips of the villi, where they tend to migrate closer to the surface. The columnar epithelial layer contains occasional infiltrating leukocytes. Paneth's cells are seen in the most basal portion of the crypts. Goblet cells are usually distributed along the middle third of the villus but occasionally are present in the crypts and on the villus tips. The average villus contains five to 30 goblet cells, varying with the length of the villus. The over-all thickness of the normal lamina propria mucosae is 1,000 to 1,500 μ.

Case Reports

Case 1 (figure 2a). This 46 year old woman was first studied in 1947 because of intense pallor, weakness, diarrhea and burning of the tongue. At that time the red blood cell count was 660,000 and the white blood cell count was 1,650. Blood studies after one transfusion showed macrocytosis with a mean corpuscular volume of 108 cubic microns. Free hydrochloric acid was present in the gastric juice. She responded to transfusions and injections of liver extract, only to be re-admitted four months later in another relapse with a red blood cell count of 430,000.

The patient's course has been characterized by irregular clinic attendance, intermittent therapy, and chronic symptoms with frequent bouts of diarrhea. She had a third relapse in 1949 (red blood cell count, 610,000) and a fourth in 1953 (red blood cell count, 2,350,000). A bone marrow specimen taken several days after treatment continued to show residual megaloblastic changes in the red cell development.

Absorption studies performed during hematologic remission in 1955 revealed a five-hour urinary xylose excretion of 3.2 gm. on one occasion and 2.2 gm. on another. Serum vitamin A values were 25 μg. and 30 μg. at five and seven hours, respectively, after the oral dose. The maximal optical density of the serum after ingestion of butter was 0.0655.

In August, 1955, the patient delivered her tenth living child. Two weeks later bilateral tubal ligation was performed under spinal anesthesia, affording the opportunity to obtain the jejunal biopsy described below. She had not taken folic acid for seven weeks prior to biopsy. Following biopsy she was given vitamin B_{12} and folic acid, with improvement, after which she followed her usual course of intermittent episodes of diarrhea. In June, 1956, a 12-day fat balance study revealed a daily average fecal fat excretion of 8.35 gm. on an average daily intake of 77 gm.

Histologic Description: 1. The villi appeared of normal length but were distorted by slight edema, clubbing, and by bridging across their tips.

2. The columnar cells showed abundant cytoplasm, numerous mitotic figures and normal numbers of goblet cells. At the tips of the villi the columnar epithelium contained nuclear fragments, possibly the remnants of inflammatory cells.

3. The lamina propria displayed mild edema, congested blood vessels and an increase in inflammatory cells, especially eosinophils and, to a lesser degree, lymphocytes and plasma cells.

4. The submucosa was edematous and the vessels were congested.

Case 2 (figure 2b). This patient had a normal pregnancy and delivery of her first child in 1953 at the age of 21. Sixteen months later, having delivered her second child, she immediately developed severe diarrhea, weight loss, pallor and burning of the tongue. When admitted to the hospital one month post partum she was anemic (hemoglobin, 5.8 gm.), the red cells were macrocytic (MCV, 125 cubic microns), and the bone marrow was megalobastic. A reticulocyte peak of 13.2% occurred after therapy with liver extract and all symptoms disappeared.

A few months later she became pregnant again and was observed carefully and frequently in the outpatient clinic. She felt well and stated she ate a nutritious diet, so that no folic acid or other therapy was prescribed during the first six months of pregnancy. During the seventh month she developed severe diarrhea, anorexia and pallor. The hemoglobin had fallen in four weeks from 9.0 gm. to 6.1 gm. Upon hospitalization she was found to have a megaloblastic bone marrow. Absorption studies at this time revealed a urinary xylose excretion of 2.3 gm., and serum vitamin A values of 10 μg. fasting, 65 μg. at five hours, and 85 μg. at seven hours. The maximal optical density of the serum after the butter test was 0.0706. A reticulocyte peak of 22.4% occurred on the ninth day after beginning folic acid therapy, and again all symptoms disappeared. Repeat xylose determinations after treatment were normal (5.0 gm. and 6.6 gm.), but the butter test and vitamin A test continued to indicate impaired absorption.

The patient did not report to the outpatient clinic during her last month of pregnancy and delivered at home, having omitted folic acid for one month. On October 14, 1956, two months after delivery, a bilateral tubal ligation was performed under spinal anesthesia, and a jejunal biopsy was obtained at the same time. At the time of this surgery the patient had no diarrhea or glossitis, and the hemoglobin was 10.2 gm., although she had not received folic acid during the previous three months.

Histologic Description: 1. The villi were of normal length but showed mild edema and clubbing. In a few areas there was marked widening of the villi: in other areas it was less marked.

2. The columnar cells had abundant cytoplasm. Goblet cells were numerous. Mitotic figures were present but did not seem increased in number. At the tips of the villi the columnar layer showed the same infiltration with nuclear fragments as noted in case 1.

3. The lamina propria showed considerable edema and a slight increase in fibrillar elements. Plasma cells and lymphocytes were increased moderately, and eosinophils were increased markedly.

4. The submucosa was not remarkable except for an infiltration of eosinophils in the muscularis.

Case 3 (figure 2c). This 42 year old female (gravida XVII, para XIV, aborta III) was first seen during the last trimester of her seventeenth pregnancy, complaining of glossitis and a severe diarrhea with over 20 bowel movements daily. There was a history of a similar episode one year earlier. Laboratory studies revealed a red blood cell count of 3.38 million and a hemoglobin value of 9.04 gm. She received symptomatic treatment and was discharged. Two months later she delivered at home, and five months later she was re-admitted, having had chronic diarrhea and intermittent burning of the tongue for 10 months. Physical examination revealed dehydration of the skin, atrophy of the lingual papillae, a cystocele and a rectocele. Laboratory studies revealed red blood cells, 3.98 million; hemoglobin, 10.9 gm.; white blood cells, 14,450, and 24% eosinophils on the blood smear. There was free hydrochloric acid in the gastric contents (70°). The red cells appeared hypochromic, but there was some macrocytosis (MCV, 97). The bone marrow at this time revealed mild megaloblastoid changes, with large intermediate and late red cell precursors and giant granulocytes. Stools contained hookworm ova. Urinary xylose excretion was 3.9 gm. in five hours, and the serum vitamin A values were 50 and 60 μg. at five and seven hours, respectively. The patient passed a daily average of 6.4 gm. of fecal fat during the 12-day study, consuming an average of 74 gm. of fat daily.

In October, three months after delivery, bilateral tubal ligation was carried out under spinal anesthesia, and at the same time a biopsy was obtained from the jejunum.

She had received folic acid, 5 mg. daily, for two weeks prior to the operation, with improvement of her symptoms. Blood counts were within normal limits at the time of surgery except for eosinophilia of 24%. She made an uneventful postoperative recovery, but has continued to have recurrent episodes of diarrhea and burning of the tongue.

Histologic Description: 1. The villi were broad-ended, quadrangular or club-shaped. There was considerable fusion at the tips of adjacent villi. There was some thinning of the mucosal layer.

2. The columnar layer showed many goblet cells. The nuclei of the columnar cells were basal, and the cytoplasm was abundant at the bases of the villi, but toward the lumen the cytoplasm became scant and the nuclei were more irregular in location and shape. Again an infiltration with nuclear remnants was seen. Mitotic figures were slightly increased in number.

3. The lamina propria contained numerous inflammatory cells, predominantly lymphocytes and eosinophils. There were an increase in fibrous elements and a moderate amount of edema. The capillaries and lymphatics appeared engorged.

4. The submucosa showed slight edema but otherwise was not remarkable.

Case 4 (figure 3a). This white male was first seen in 1955, at the age of 47, complaining of (1) pain and weakness in both legs of eight years' duration, and (2) chronic severe diarrhea of five years' duration. Because of claudication, trophic changes, absent or diminished arterial pulsations in the legs and a history of heavy smoking, a diagnosis of Buerger's disease was made. It was learned that the patient had from five to 20 bulky, fetid bowel movements daily, a complaint which he found less troublesome than the disability in his legs. There was no history of pallor or burning of the tongue. Laboratory studies revealed red blood cells, 4,050,000; hemoglobin, 12.9 gm.; white blood cells, 5,900. The mean corpuscular volume of red cells was 103. A bone marrow showed a slight increase in mature plasma cells but no other abnormality. The gastric juice contained free hydrochloric acid. The prothrombin time, bilirubin, calcium and chest x-ray were normal. On a 12-day fat balance program he ate an average of 56 gm. of fat daily and excreted a daily average of 22.5 gm. The five-hour urine xylose excretion was 2.5 gm. Blood levels of vitamin A were 30 and 35 μg., five and seven hours after an oral dose.

A lumbar sympathectomy was recommended in view of constant severe leg pain requiring narcotics for relief. A transabdominal approach was decided upon to determine if Whipple's disease or some related process was producing steatorrhea. Biopsies were taken of a mesenteric lymph node and the jejunum, and a unilateral lumbar sympathectomy was performed. He recovered uneventfully but continued to have leg pain and diarrhea.

He was given folic acid, which produced no reticulocytosis or clinical improvement. The addition of cyanocobalamine was followed by an increase in reticulocytes to 2.6% on the fifth day but no other remarkable change. A two-week course of cortisone therapy was without benefit. Six months after the sympathectomy, vitamin therapy was discontinued and he was given five-day successive courses of succinylsulfathiazole, oxytetracycline and chloramphenicol. This produced a dramatic but transitory decrease in diarrhea and was associated with normal stool fat for a five-day period. The diarrhea returned with only two to three stools daily; the patient has gained weight (from 92 to 102 pounds), and during the last six months he has been generally improved without further therapy.

Histologic Description: 1. There was a marked irregularity of the villi, some of which were shorter than normal. Clubbing was more prominent than coalescence of villi, but even the bases appeared broader than normal.

2. The columnar layer was well preserved, even on the villus tips, and the nuclei were regular in shape and position. The cytoplasm was normal in amount. Goblet

cells were much increased, being present even on the tips of the villi. Mild infiltration with inflammatory nuclei was present but was less than in previous patients.

3. The lamina propria was packed with inflammatory cells except in areas where the marked edema greatly dispersed them. Here the eosinophils, neutrophils, lymphocytes and plasma cells were quite prominent. There was a moderate increase in fibrous strands. Blood vessels and lymphatics were dilated and prominent. There was no evidence of Whipple's disease or Buerger's disease.

4. The submucosa was quite edematous, and there was a slight increase in lymphocytes and plasma cells.

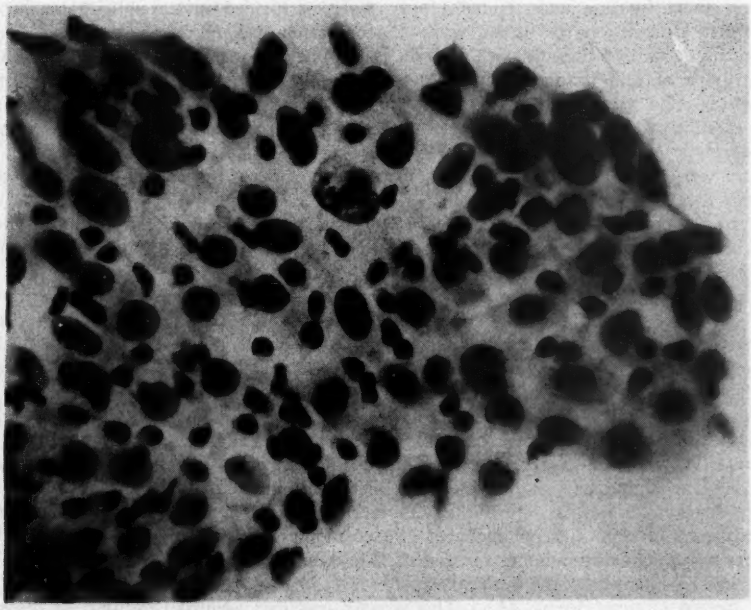

FIG. 6. Case 5. A portion of the columnar epithelium, obtained by gentle curettage at the time of surgery, smeared and stained by the Papanicolaou technic. × 440.

The lymph node biopsy revealed moderate reticuloendothelial hyperplasia and scattered calcific flecks. No foam cells or periodic acid-Schiff staining material was present.

Case 5 (figures 3b, 4b, 5b and 6). This patient was hospitalized in 1953, at the age of 23, for diarrhea, burning of the tongue and pallor during the seventh month of her fourth pregnancy. She had a macrocytic anemia and was given folic acid, liver extract, vitamin B_{12} and a blood transfusion. The reticulocyte count was 10.4% on the seventh day of therapy, and she was discharged improved on the twelfth hospital day. Blood values were normal at the time of delivery two months later.

She was next seen in 1956, at the age of 26 (gravida VIII, para IV, aborta IV), two months post partum. She complained of weakness, burning of the tongue, progressive pallor and diarrhea associated with cramping abdominal pains. She stated she had received liver injections for one month, without improvement. Physical examination revealed a poorly nourished female weighing 83 pounds, with pallor,

a smooth red tongue and a distended abdomen. Laboratory studies were: red blood cells, 1.78 million; white blood cells, 4,500; hemoglobin, 5.4 gm. Reticulocyte count was 5.7%; mean corpuscular volume, 127. The bone marrow showed erythroid hyperplasia, large numbers of typical megaloblasts and giant neutrophils. Free hydrochloric acid was present in the gastric juice. The xylose excretion was 0.8 gm. Serum vitamin A was 35 μg., and 40 μg. at five and seven hours, respectively, after the oral test dose. On a 12-day study the patient excreted an average of 16.4 gm. of fecal fat daily. During the fourth week in the hospital she was given two transfusions of whole blood, after which the hemoglobin was 7.1 gm. Another transfusion was given in preparation for surgery. Five weeks after admission, bilateral tubal ligation and jejunal biopsy were performed under spinal anesthesia. A fourth transfusion was given while the operation was in progress. The patient was then started on therapy with vitamin B_{12}. The postoperative course was smooth. The diarrhea and flatulence disappeared promptly and she developed a ravenous appetite. She was placed on folic acid therapy, 5 mg. daily, and discharged. After two months of treatment the hemoglobin was 13.6 gm., and she had gained 32 pounds in weight. At this time the xylose test gave a value of 4.1 gm. and the vitamin A values were 150 μg. and 225 μg. at five and seven hours, respectively, after the test dose.

Histologic Description: 1. The villi were shortened, broad-ended and quite wide. The over-all thickness of the mucosal layer was slightly reduced. On serial section the crypts were found to be quite tortuous.

2. The cytoplasm of the columnar cells was abundant in the crypts but diminished rapidly toward the lumen. On the free surface the columnar layer was markedly infiltrated with nuclear fragments, presumably from inflammatory cells. Here the cytoplasm was thin and highly vacuolated. The columnar cells were flattened and almost cuboidal in appearance. In the crypts, mitoses appeared to be approximately normal in number. The nuclei varied in shape and staining, and a few of the crypt nuclei were quite large and pale. Paneth's cells appeared to be normal. Goblet cells were quite large but did not appear to be increased in number.

3. The lamina propria was densely filled with inflammatory cells and occupied more space than normal, since the villi were fused. The inflammatory cells were chiefly plasma cells and lymphocytes, the eosinophils being only slightly increased. There was a moderate amount of edema. The lymphatics were quite dilated.

4. The submucosa was not remarkable.

Case 6 (figures 3c and 4c). This woman was first admitted in 1952, at the age of 39, because of diarrhea, weight loss, pallor and glossitis which had started six months before during the last trimester of her fifth pregnancy. At the time of admission, four months after delivery, the red blood cell count was 2.21 million, the hemoglobin was 9.5 gm., and there was evident macrocytosis (MCV, 127). The bone marrow was frankly megaloblastic. She responded to daily injections of vitamin B_{12}, showing a reticulocyte peak of 13.2% and marked clinical improvement. She was seen regularly in the outpatient clinic and received adequate maintenance therapy with either folic acid or vitamin B_{12}, in spite of which she continued to have occasional episodes of diarrhea and glossitis. Her diet was described as very poor. Absorption studies in 1955 performed during hematologic remission revealed a xylose excretion of 2.9 gm., and vitamin A levels of 15 μg. fasting, 35 μg. at the fifth hour, and 35 μg. at the seventh hour after the oral test dose. Free hydrochloric acid was present in the gastric juice after histamine stimulation.

The patient became pregnant again and delivered her sixth child in September, 1956. The xylose test was normal at this time, but the vitamin A test again showed impaired absorption. On the ninth postpartum day bilateral tubal ligation was performed and at the same time a jejunal biopsy was obtained. Blood values were

normal at the time of surgery, but she had not received folic acid or other specific therapy for the last four months.

Histologic Description: 1. The villi were of normal length, but many were broad-ended and edematous at the tip. Many villi were two to three times the normal width.

2. The columnar cells appeared to be diminished in number toward the villus tips and showed some vacuolation and increase in inflammatory cells. Goblet cells were present in average numbers. Mitoses were rather numerous.

3. The lamina propria showed an increased inflammatory cellularity and mild edema. There was an increase in plasma cells and polymorphonuclear leukocytes.

4. A few dilated lymphatics were visible in the submucosa. The muscle and other structures appeared to be normal.

Case 7 (figure 7). This 38 year old female was admitted two months after the uncomplicated delivery of her eighth full term living child. Two days post partum she developed vomiting, abdominal cramps and a chronic diarrhea, with six to eight

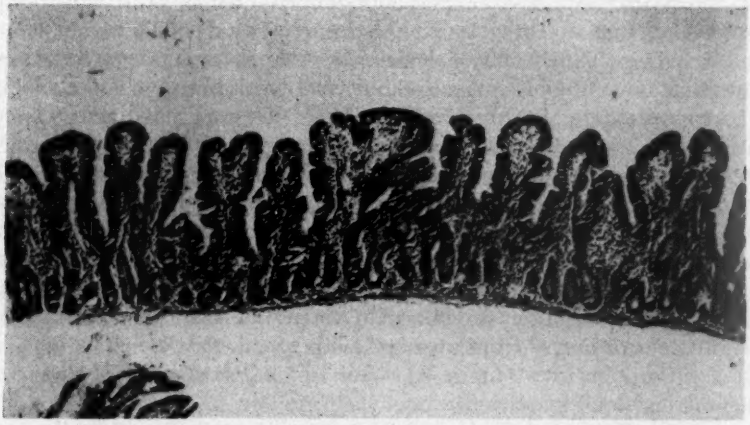

FIG. 7. A section of jejunum from case 7, a patient with megaloblastic anemia of pregnancy who had normal absorption tests.

large bowel movements daily. She denied burning of the tongue, but she did notice dizziness, exertional dyspnea and ankle swelling several days before admission, at which time the hemoglobin was 3 gm., and a transfusion was given. Blood studies the next day revealed red blood cells, 1,130,000; hemoglobin, 4.45 gm.; white blood cells, 2,650; platelets, 84,000; reticulocytes, 3.3%. The red cells were macrocytic (MCV, 132), and the marrow showed a full-blown megaloblastic pattern. There was no free hydrochloric acid on gastric analysis. The xylose test showed a five-hour urinary excretion of 5.0 gm. The serum vitamin A was 25 μg. fasting and rose to 190 and 170 μg. five and seven hours, respectively, after an oral dose of 300,000 units of vitamin A. On a 12-day fat balance study she excreted 4.93 gm. of fat in the feces while consuming a daily average of 79 gm. of fat.

The diarrhea subsided and the patient improved soon after admission with no therapy other than the hospital diet. There was a reticulocytosis of 9% on the tenth hospital day. Three weeks after admission she was given a 500 c.c. blood transfusion, after which the hemoglobin was 10.8 gm. A bilateral tubal ligation and jejunal biopsy were then performed, followed by an uneventful recovery. Immediately after the operation the patient was placed on 30 μg. of vitamin B_{12} daily.

A Schilling test for intrinsic factor was done at this time and gave a normal result (24% of an oral dose of Co^{60} vitamin B_{12} was excreted in a 24-hour urine). When discharged six weeks after admission she felt perfectly well and has remained asymptomatic.

Histologic Description: 1. The villi were generally slender and of average length. Occasional "double villi" were seen, with slight edema.

2. The columnar layer showed average numbers of mitoses. The columnar cells were normal in number but showed an increase in inflammatory cell infiltration. Goblet cells were normal in number.

3. The lamina propria displayed essentially normal cellularity and vascularity.

4. The submucosa was essentially normal.

Discussion

In the preparation of this report it soon became apparent that there is little information available on the appearance of the normal human small intestine. Standard textbooks depict selected portions of human or animal small bowel, sometimes only a single villus or crypt. Pathology texts pay scant attention to the histology of the normal small bowel, and pathologists so seldom encounter freshly fixed specimens that they have grown accustomed to seeing autolytic degeneration. In particular, the range of variation in histology among a group of normal subjects is ill-defined. Our experience is thus similar to Paulley's. The observations made here are based on the comparison of the sprue biopsies with 15 control biopsies. It is apparent from the descriptions and photomicrographs that the biopsies from patients with malabsorption show edema, inflammation, and changes in the number and contour of villi. The absence of such changes in normals and in a control biopsy from a patient with megaloblastic anemia who had normal absorption tests (figure 7) tends to validate the use of these tests in estimating small bowel function.

1. *Villi; Absorptive Surface:* An important feature shared by the sprue biopsies is a considerable decrease in absorptive surface area. This is attendant on widening of villi and an apparent coalescence of adjacent villi. One also notes a shortening of the free ends of the villi or, expressed in another way, a thickening of the crypt portion which is not in direct contact with the luminal contents. On examination of serial sections in case 5 it was observed that the crypts are considerably more tortuous than in the normal. The delicate ruffling of the columnar layer seen in controls is not found in the patients with malabsorption.

An attempt was made to measure the degree of loss in absorptive surface area. Photomicrographs from the untreated subject and a normal (figures 1a and 3b) were made and greatly enlarged under identical conditions. The length of the columnar layer was measured by overlaying with string. For comparable lengths of intestine the length of the columnar layer in cross section was three times as long in the normal as in the untreated patient. Under similar conditions the length and diameter of individual villi were measured with a ruler. From these figures the surface area was estimated

using the formula for the surface of a cylinder. It was found that for identical squares of bowel (measured at the muscularis mucosae), the surface area of the normal was about four times greater than in the untreated sprue subject. While this is a considerable difference, it should be noted that a simple loss in absorptive surface area is not of itself an adequate explanation for the malabsorption observed in sprue. Althausen et al.[16, 17] have reported three patients who survived massive resection of the small bowel and later achieved nutritional equilibrium. One of these patients retained only 45 cm. of small bowel, or 10% of its original length. A number of compensatory mechanisms must exist in normal individuals. A decrease in absorptive surface area must, however, be considered a contributory factor in the malabsorption observed in the present group of cases. This is particularly true if the entire length of jejunum is involved, as it probably is.

2. *Lamina Propria:* A second prominent feature present in all of the biopsies was inflammation of the lamina propria. While it is recognized that neutrophils, eosinophils, lymphocytes and plasma cells are normally present in the lamina propria, the normal quantity was greatly exceeded in the patient material. In certain cases the lamina propria was densely packed with these cells. Eosinophils and plasma cells contributed most to the increased cellularity. No correlation could be found, however, between the eosinophil counts in the peripheral blood and those in the villi. One patient with marked eosinophilic infiltration of the bowel (case 4, figure 3a) had absolute eosinophil counts of 333 and 536 per cubic millimeter, and the stool was negative for parasites. Another patient (case 3, figure 2c), with 24% eosinophils on the blood smear and Uncinaria in the stool, showed minimal numbers of eosinophils in the intestinal section.

Although atrophy of the intestinal mucosa has been emphasized in previous reports, marked thinning of the lamina propria was not encountered in our series. In four cases the mucosal layer was just as thick as in normals, while in the remaining two the lamina propria was not less than 75% of normal thickness. The widening of villi makes thinning more apparent than real. Severe malnutrition and distention of the intestine by gas prior to autopsy presumably account for some of the atrophy reported by earlier authors. This interpretation was considered by Bahr,[2] who did not believe atrophy was a specific feature of sprue. Hyaline degeneration of the villi, as described by Schein,[4] was not encountered in this series. The surgeon noted no gross pathology in these biopsies except for evidence of edema in the bowel wall in case 4.

On microscopic examination, edema was present in every specimen, usually limited to the lamina propria but in a few cases involving the submucosa as well. The most marked edema was in the villi of case 4, where fluid collection permitted ready evaluation of the inflammatory cytology. The untreated subject (case 5) showed minimal edema of the villi and marked distention of the lymphatics, but no edema of the submucosa.

3. *Columnar Epithelium:* Examination of the columnar epithelium revealed an increase in goblet cells in four of the seven individuals as compared with the controls. This is in accord with the observation of Frazer [18] that an increase in small bowel mucus may account for the clumping of barium sulfate seen on radiologic study in these patients. However, the very patient in whom increased goblet cells would have been expected (case 5) did not show it. Unfortunately, radiologic examination was not obtained in this patient.

Figure 4b illustrates the appearance of the columnar epithelium in an untreated subject. In contrast with normal controls, this specimen exhibits a flattening of the cells, marked vacuolation of the columnar cytoplasm, nuclear debris and, indeed, a paucity of columnar nuclei. Here the normal columnar layer with abundant cytoplasm and nuclei in palisades has given way to a thin shell of cell remnants. The nature of the irregular dark staining nuclear fragments is not known. They appear to be remnants of leukocytes, but presumably they could also be due in part to columnar cell degeneration. The marked vacuolation was not recognized until after the entire specimen had been embedded in paraffin for section, so that it was not possible to do fat stains. In the next biopsy (case 6), vacuolation was noted in the columnar cells, but frozen sections stained with Sudan IV did not reveal fat particles in the epithelial layer, although fat droplets elsewhere were stained. This single observation is not interpreted as excluding the possibility that some of the fecal fat is derived from desquamation of intestinal cells. It is of interest that Bahr noted vacuolation and degeneration of the jejunal glandular epithelium over 40 years ago. Somewhat similar but less marked changes were noted in the columnar layer of all sprue cases except one (case 4). This man differed from all the others in that he had never been anemic and did not have megaloblastic marrow changes in spite of unquestionable malabsorption.

Papanicolaou's smears of the jejunal epithelium were prepared in several instances, but they are difficult to evaluate in the absence of control material. Figure 6 represents a portion of epithelium from case 5, and shows nuclei that are larger and paler than any seen in similar preparations from two treated subjects. This photograph also illustrates the inflammatory infiltration in the columnar layer.

4. *Submucosa:* The submucosa was essentially normal in the untreated subject, but showed slight to marked edema and congestion of vessels in the other subjects. The muscularis layer was histologically normal in all cases except case 2 where it showed a perivascular infiltration with eosinophils. There was no consistent finding in the submucosa to offer an explanation for the altered motility of the bowel in sprue patients.

5. *Physiologic Considerations and Interpretations:* It is not possible at this time to ascribe specificity to the pathologic changes noted here in connection with sprue. It has been well documented [19] that starvation may

produce epithelial changes and profound atrophy of the intestine, but these reports are based on autopsy material. It cannot be said that severe malnutrition in the usual sense was a problem in any of the subjects studied here. Whipple's disease produces large clubbed villi and increased goblet cells, but is characterized by foam cells bearing glycoprotein in the mucosa. This was not found in these biopsies. It has been stated by Ungley [20] and Faber [21] that the small intestine is normal in pernicious anemia, a point which may prove to be of diagnostic value in distinguishing sprue from pernicious anemia in the tropics.

In a search for a rational explanation for the malabsorption and pathologic changes which have been observed in sprue, it is pertinent to call attention to the rapid rate of cell renewal in the intestinal epithelium. The fundamental concepts were recognized in 1888 by Bizzozero,[22] who described the origin of the goblet cells in the crypts and followed their progress along the villi until they were ultimately sloughed from the tip. Similar phenomena were noted by Friedman [23] in a study of recovery from radiation. Experimental evidence in support of this has been offered by Leblond et al.,[24] who demonstrated by radioautographs that P^{32} is incorporated in the base of the rat villus and subsequently migrates toward the tip. A number of studies indicate that the time required to replace the intestinal epithelium in laboratory animals is from two to three days.[25] Detrick et al.[26] found evidence for a rapid turnover in observing apparent histologic recovery in rat small intestine by the third day after irradiation, although malabsorption of glucose persisted for several days longer. It has been observed that the mitotic rate of the small intestine continues at a rather constant high level, whereas other tissues show a fluctuation according to the availability of nutrients, particularly glucose.[27]

The survival time of the human columnar epithelium is not known, but there is some evidence that it is short. For example, agents which inhibit mitosis, such as colchicine, nitrogen mustard and radiation, often produce diarrhea and other gastrointestinal symptoms promptly. In the case of colchicine, which arrests mitosis at the metaphase, there is a latent interval of several hours between the administration of a toxic dose and the onset of symptoms. This does not vary with either dosage or route of administration,[28] suggesting that symptoms may be related to the failure of new cells to appear rather than to a direct action of the drug. Folic acid antagonists act more slowly in producing in humans diarrhea, megaloblastic marrow changes, and alterations in the hair, tongue and buccal epithelium. On the other hand, the gastrointestinal symptoms of patients with sprue often show dramatic improvement within 24 to 48 hours of therapy with folic acid or vitamin B_{12}.

Cytologic studies by Gardner [29] have revealed abnormalities in the gastric columnar epithelium and in desquamated squamous cells found in the stomach, suggesting a widespread epithelial disturbance in sprue. Similar

changes have been noted in pernicious anemia.[30] During the course of the present study, observations were made on the squamous epithelium of normal persons and of patients with untreated and treated tropical sprue. Ample material was easily obtained by everting the lower lip and gently scraping the surface with the edge of a glass slide. The slides were fixed and stained by the Papanicolaou technic. It was found that in those patients with megaloblastic marrow the nuclei were larger and paler than they were in normal controls, in many cases over twice as large. With a micrometer disc in the microscope eyepiece the minimal nuclear diameter was measured for 20 unselected consecutive nuclei, with the following results:

		Mean	Standard Deviation
Normals	(35)	4.5 units	0.6
Treated sprue	(8)	4.9 units	0.7
Untreated sprue	(13)	5.6 units	0.7

The appearance is illustrated in figure 8. A similar change was noted by Rubin in a case of megaloblastic anemia of pregnancy.[31] The weight of evidence now favors the presence of cytologic abnormality in a number of different sites where rapid cellular proliferation occurs.

The interpretation therefore presents itself that at least some of the pathologic changes observed in jejunal biopsies from sprue patients result from disturbances in the epithelial surface. Either diminished production or shortened survival of columnar cells could, by jeopardizing the integrity of this surface, lead to all the changes noted. It would seem likely that intestinal involvement may be only part of a diffuse process which also affects bone marrow and other tissues. Whatever the underlying disorder, the

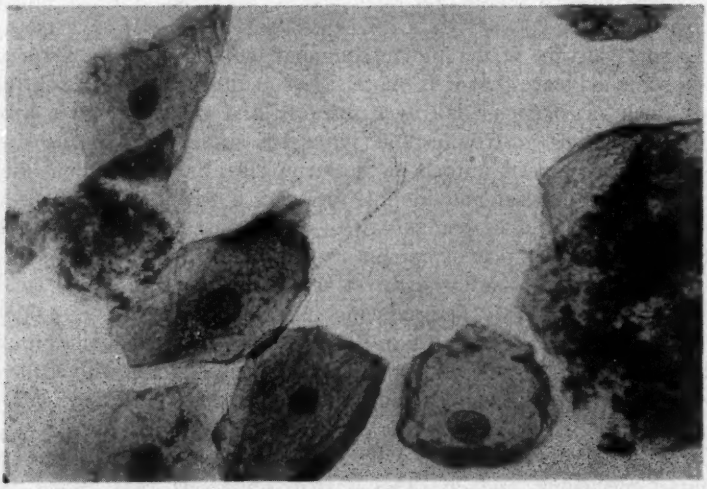

FIG. 8. A group of squamous epithelial cells from the buccal mucosa of a patient with tropical sprue in relapse. The normal appearance is represented by the cell in the upper left corner.

present study demonstrates that pathologic changes do exist in the small bowel of patients with sprue. The findings suggest the desirability of continued studies with jejunal biopsies. The advent of the functional small bowel biopsy tube described by Shiner [32] may prove to be of great value in this connection.

Summary

1. Biopsies of jejunum were obtained in six cases of sprue. Histologic study in comparison with controls revealed edema, inflammation and widening of villi in each case. Five of the six subjects displayed inflammatory infiltration of the columnar epithelium.

2. The role of faulty epithelial regeneration is discussed as a possible etiologic mechanism for the histopathology observed.

Addendum

Since the above article was submitted it has come to our attention that Milanés et al.[33] have reported on jejunal biopsy findings in a case of untreated sprue from Cuba. This specimen showed short, thick Kerkring valves, and shortening and thickening of the villi. A lymphoplasmocytic infiltration was present in both the epithelium and the lamina propria. These authors also called attention to thickening of Auerbach's plexus and degenerative changes in neurons.

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Summario in Interlingua

Depost multe annos, le opiniones relative al presentia de alterationes pathologic in le intestino tenue de patientes de sprue ha essite in conflicto le unes con le alteres. Pro evitar le difficultate additional de artefactos occurrente post morte, Paulley studiava in 1954 biopsias ab duo patientes con steatorrhea idiopathic e trovava edema, inflammation, e villos allargate. Recentemente biopsias jejunal esseva obtenite durante laparotomias pro altere causas ab sex portoricanos con malabsorption demonstrate. In comparation con casos de controlo normal, omne le specimens monstrava edema, infiltration del lamina proprie con cellulas a inflammation chronic, e villos de largor anormal. Tenuification del mucosa non esseva un aspecto prominente. Cinque del sex specimens exhibiva infiltration inflammatori, vacuolation, e tenuification del strato columnar mesme. Il es possibile que isto esseva relationate a anormalitates cytologic que occurre cognoscitemente in le epithelio squamose, le epithelio gastric, e le medulla ossee de patientes de sprue. Estimationes del area de superficie absorptive indica que il resulta un reduction de illo que poterea esser un factor contributori in le disveloppamento del syndrome de malabsorption. Le constatationes rejice definitemente le opinion que le intestino in casos de sprue es histologicamente normal. Un patiente

additional con anemia megaloblastic de pregnantia e normal tests de absorption non exhibiva le pathologia mucosal observate in le biopsias ab patientes de sprue. Es a sperar que futur investigationes pathologic va resultar in un plus precise differentiation inter le varie causas de malabsorption.

BIBLIOGRAPHY

1. Paulley, J. W.: Observations on the aetiology of idiopathic steatorrhea, Brit. M. J. **2**: 1318 (Dec. 4) 1954.
2. Bahr, P. H.: A report on researches on sprue in Ceylon 1912–1914, 1915, Cambridge University Press, London.
3. Thaysen, T. E. H.: "Non tropical sprue," 1932, Oxford University Press, London.
4. Schein, J.: Syndrome of non-tropical sprue, Gastroenterology **8**: 438, 1947.
5. Thin, G.: Psilosis (Linguae et mucosae intestini), Brit. M. J. **1**: 1358–1361 (June 14) 1890.
6. Faber, K.: Ein Fall chronischer Tropendiarrhoe ("Sprue") mit anatomischer Untersuchung des Digestionstraktus, Arch. f. Verdauungskr. **9**: 333, 1904.
7. Justi, K.: Zur Methodik der Chinindarseichung bei Malaria, Arch. f. Schiffs- u. Tropen-Hyg. **17**: 505, 1913.
8. Mackie, F. P., and Fairley, N. H.: The morbid anatomy of sprue, Indian J. M. Research **16**: 799, 1928–1929.
9. Thaysen, T. E. H.: Pathological anatomy of the intestinal tract in tropical sprue, Tr. Roy. Soc. Trop. Med. and Hyg. **24**: 539, 1931.
10. Fairley, N. H.: Tropical sprue with special reference to intestinal absorption, Tr. Roy. Soc. Trop. Med. and Hyg. **30**: 9, 1936.
11. Suarez, R. M., Spies, T. D., and Suarez, R. M., Jr.: The use of folic acid in sprue, Ann. Int. Med. **26**: 643, 1947.
12. Adlersberg, D., and Schein, J.: Clinical and pathologic studies in sprue, J. A. M. A. **134**: 1459, 1947.
13. Hernandez-Morales, F., and Noya, J., cited by Rodriguez-Molina, R. R.: Sprue in the Puerto Rican indigent, Bol. Asoc. méd. de Puerto Rico **32**: 187, 1940.
14. Gardner, F. H., and Perez-Santiago, E.: Oral absorption tolerance tests in tropical sprue, Arch. Int. Med. **98**: 467, 1956.
15. Van der Kamer, J. H., Huinink, H. ten B., and Weyers, H. H.: A rapid method for the determination of fat in feces, J. Biol. Chem. **177**: 347, 1949.
16. Althausen, T. L., Uyeyama, K., and Simpson, R. G.: Digestion and absorption after massive resection of the small intestine. I. Utilization of food from a "natural" versus a "synthetic" diet and a comparison of intestinal absorption tests with nutritional balance studies in a patient with only 45 cm. of small intestine, Gastroenterology **12**: 795, 1949.
17. Althausen, T. L., Doig, R. K., Uyeyama, K., and Weiden, S.: Digestion and absorption after massive resection of the small intestine. II. Recovery of the absorptive function as shown by intestinal absorption tests in two patients and a consideration of compensatory mechanisms, Gastroenterology **16**: 126, 1950.
18. Frazer, A. C.: Disordered gastro-intestinal function and its relationship to tropical sprue, coeliac disease, and idiopathic steatorrhea, Tr. Roy. Soc. Trop. Med. and Hyg. **46**: 576, 1952.
19. Larsen, H., Hoffmeyer, H., Kieler, J., Thaysen, E. H., Thaysen, J. H., Thygesen, P., and Wulff, M. H.: Hunger diarrhoea—famine disease in German concentration camps —complications and sequels, Acta med. Scandinav., Supp. 274, **144**: 147–148, 1952.
20. Ungley, C. C.: The chemotherapeutic action of vitamin B_{12} *in* Vitamins and Hormones, Vol. 13, edited by Harris, R. S., Marrian, G. F., and Thimann, K. V., 1955, Academic Press, New York, p. 189.

21. Faber, K.: Lectures on internal medicine, 1927, Hoeber & Co., New York.
22. Bizzozero, G.: Über die Regeneration der Elemente der Schlauchformigen Drusen und des Epithels des Magendarmkanals, Anat. Anz. **3**: 781, 1888.
23. Friedman, N. B.: Cellular dynamics in the intestinal mucosa: the effect of irradiation on epithelial maturation and migration, J. Exper. Med. **81**: 553, 1945.
24. Leblond, C. P., Stevens, C. E., and Bogoroch, R.: Histological localization of newly-formed desoxyribonucleic acid, Science **108**: 531, 1948.
25. Leblond, C. P., and Walker, B. E.: Renewal of cell populations, Physiol. Rev. **36**: 255, 1956.
26. Detrick, L. E., Upham, H. C., Highby, D., Debley, V., and Haley, T. J.: Influence of x-ray irradiation on glucose transport in the rat intestine, Radiation Research **2**: 483, 1955.
27. Bullough, W. S.: Hormones and mitotic activity, *in* Vitamins and Hormones, Vol. 13, edited by Harris, R. S., Marrian, G. F., and Thimann, K. V., 1955, Academic Press, New York, p. 262.
28. Goodman, L. S., and Gilman, A.: The pharmacological basis of therapeutics, 2nd Ed., 1955, The Macmillan Co., New York.
29. Gardner, F. H.: Observations on the cytology of gastric epithelium in tropical sprue, J. Lab. and Clin. Med. **47**: 529, 1956.
30. Graham, R. M., and Rheault, M. H.: Characteristic changes in epithelial cells in pernicious anemia, J. Lab. and Clin. Med. **43**: 235, 1954.
31. Rubin, C. E.: The diagnosis of gastric malignancy in pernicious anemia, Gastroenterology **29**: 563, 1955.
32. Shiner, M.: Jejunal-biopsy tube, Lancet **1**: 85 (Jan. 14) 1956.
33. Milanés, F., León, P., and Causa, A.: Jejunum histopathological studies through surgical biopsy in a case of tropical sprue in relapse, Rev. Gastroenterol. **18**: 182, 1951.

MALABSORPTION SYNDROME: INTESTINAL ABSORPTION OF VITAMIN B_{12}* †

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The common denominator of the clinical entities variously known as non-tropical sprue, tropical sprue, celiac disease and idiopathic steatorrhea is impaired intestinal absorption of various dietary substances. The etiology of these syndromes is not known, but evidence for a hereditary predisposition as well as environmental factors has been documented. In the broader view of today, these several clinical entities may be grouped together under the term "malabsorption syndrome" and considered a complex metabolic disorder, the focal point of which is disturbed intestinal absorption.[1] In addition to primary malabsorption syndrome, somewhat similar clinical pictures may be seen in intestinal resection, blind loop syndrome, and certain disorders which involve the intestinal tract, such as lymphosarcoma and intestinal lipodystrophy. These secondary types of "sprue" show, in contrast to primary malabsorption syndrome, gross pathologic alterations of the intestinal tract.

In both the primary and the secondary malabsorption syndromes, characteristic changes in the hematologic picture may be encountered.[2] In its severest form, the hematologic picture of the malabsorption syndrome consists of megaloblastic erythropoiesis in the marrow, with pancytopenia, including macrocytic anemia, in the peripheral blood. In its mildest form, the hematologic picture may still continue to show macrocytosis of the red cells, without anemia or pancytopenia, and with an apparently normal bone marrow.[3] This characteristic blood picture may be altered in specific instances by superimposed deficiencies (e.g., that of iron), or by complications (e.g., blood loss, infection).[2]

The development of the anemia of primary malabsorption syndrome is generally attributed to impaired absorption of dietary elements necessary for normal hematopoiesis. Normal hematopoiesis demands, *inter alia,* the presence in a normally functioning marrow of adequate precursor materials,

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notably protein, iron, folic acid and vitamin B_{12}, as well as other metabolic materials such as ascorbic acid. In primary malabsorption syndrome it is generally believed that a lack of certain of these materials in the marrow, due to defective absorption of these substances from ingested food, results in abnormal hematopoiesis and, specifically, in megaloblastic erythropoiesis.

This report is concerned with the abnormality of absorption of one of these factors, vitamin B_{12}, in the malabsorption syndrome, and the relationship of this absorptive defect to the pathogenesis of the anemia of sprue.

Materials

Twenty-five patients with idiopathic sprue were studied. The diagnosis was made on the basis of the typical clinical picture, supplemented by x-ray studies of the gastrointestinal tract, studies of absorption and excretion of fat, and tests for intestinal absorption of glucose and vitamin A.[4, 5] Details have been presented elsewhere.[4]

In addition, three cases of sprue secondary to resection of the small bowel (for jejuno-ileitis in two cases, for superior mesenteric artery occlusion in one case) were studied.

Three cases were also studied in which a spruelike syndrome (diarrhea, steatorrhea, macrocytic anemia) was present in patients with blind intestinal loops.

Methods

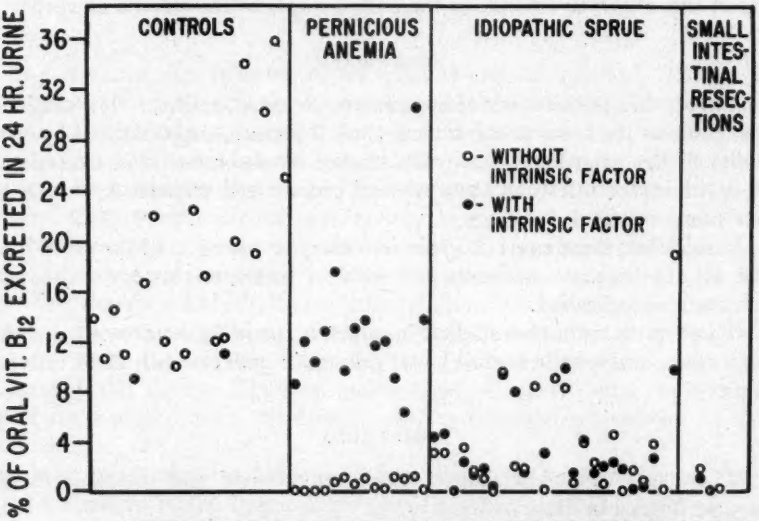
The usual clinical, roentgenologic, hematologic and metabolic studies were performed in these patients.[4]

The intestinal absorption of vitamin B_{12} was estimated by means of a modification of the urinary excretion test of Schilling.[5, 6] A standard tracer dose of labeled vitamin B_{12} (Co^{58} or Co^{60}) was given by mouth in the early morning following 12 to 16 hours of fasting.* The dose was 0.4 to 0.5 μg. of vitamin B_{12}, an amount in the physiologic range. Immediately after the ingestion of the labeled vitamin B_{12} a parenteral injection of nonradioactive vitamin B_{12}, 1,000 μg. in amount, was given subcutaneously or intramuscularly. The urine was collected for the following 24 hours, and its content of radioactivity was determined by counting a 500 c.c. aliquot of the urine by means of a thallium-activated sodium iodide crystal scintillation counter. The ratio of the amount of radioactivity in the 24-hour collection of urine to the radioactivity in the test dose (determined each time by use of an appropriate standard) was then calculated.

Normal individuals showed an average excretion of 17.9% of the ingested radioactivity (figure 1), with a range from 9% to 36%. In 15 patients with proved pernicious anemia the average excretion was 0.5%,

* We are indebted to Dr. Nathaniel Ritter and Dr. Charles Rosenblum, Merck Institute for Medical Research, Rahway, New Jersey, for generous supplies of radioactive vitamin B_{12}.

with a range of 0 to 1.2%. Investigations elsewhere [7] have shown that, in normals, the 24-hour excretion of radioactivity in the urine represents approximately one third of the amount of vitamin B_{12} absorbed through the intestinal tract, so that the average normal individual in our group absorbed 53% of the oral dose (i.e., approximately 0.25 μg.). Patients with pernicious anemia showed no significant absorption.



	CONTROLS	PERNICIOUS ANEMIA		IDIOPATHIC SPRUE		SMALL INTESTINAL RESECTIONS	
	NO I.F. (o)	NO I.F. (o)	I.F. (•)	NO I.F. (o)	I.F. (•)	NO I.F. (o)	I.F. (•)
AVERAGE	17.9	0.5	12.9	3.6	3.3	0.63	0.6
RANGE	9-36	0-1.2	6.3-30.5	0-19	0-10	0-1.8	0-1.1

FIG. 1. Excretion tests in control subjects and in patients with pernicious anemia, idiopathic sprue and extensive intestinal resections. The open circles represent the excretion of labeled vitamin B_{12} given orally. The closed circles represent the excretion of labeled vitamin B_{12} given orally *with* intrinsic factor. Each test on the same patient is placed in vertical alignment.

In most patients the above test was repeated, after an interval of one week or more, with the addition of a potent intrinsic factor by mouth.* Intrinsic factor had no effect on the amount of urinary radioactivity in the normal individuals. In the patients with pernicious anemia the effect of intrinsic factor was to raise the amount of urinary radioactivity toward normal, to an average value of 12.9% of the ingested dose (range, 6.3 to 30.5%).

* Generously supplied by Dr. Osterberg, Abbott and Co., Chicago, Illinois (Lot No. E-5872; 30 mg. was used in each test).

Results

The urinary excretion of labeled vitamin B_{12} is shown in figure 1 and table 1.

In the group of 25 patients with idiopathic malabsorption syndrome the average excretion of radioactivity was 3.6% (range, 0 to 19%). Of this group, 20 showed marked impairment of intestinal absorption of vitamin B_{12}, four had low normal results, and one was entirely normal (table 1). The test was repeated with intrinsic factor in 22 patients; the average excretion was 3.3% (range, 0 to 10%).

The three patients with sprue secondary to intestinal resection showed no absorption of the orally administered vitamin B_{12} (urinary excretion, 0 to 1.8%). Retesting with intrinsic factor was done in two patients and showed no change.

Table 1

Results of the Urinary Excretion Test in 31 Patients with Primary and Secondary Malabsorption Syndrome. Values represent the percentage of the oral dose of vitamin B_{12} which appeared in the urine in 24 hours (see text)

Patient	Vit. B_{12} Alone	Vit. B_{12} with Intrinsic Factor	
A. Primary Malabsorption syndrome:			
1.	3.0	4.4	
2.	3.1	4.6	
3.	0.0	0.0	
4.	3.5	2.4	
5.	1.6	1.4	
6.	1.0	1.8	
7.	0.0	0.3	
8.	9.6	9.5	
9.	2.0	8.0	
10.	1.9	1.6	
11.	8.5	—	
12.	0.5	3.1	
13.	9.1	—	
14.	8.3	10.0	
15.	0.7	1.5	
16.	3.9	4.1	
17.	2.3	1.5	
18.	0.6	2.0	
19.	4.6	2.4	
20.	0.5	1.9	
21.	1.7	0.2	
22.	0.9	0.4	
23.	3.8	2.7	
24.	0.2	—	
25.	19.0	9.8	
B. Intestinal Resections:			
26.	1.8	1.1	
27.	0.0	0.0	
28.	0.1	—	
C. Blind Loop Syndrome:			
29.	2.6	—	(12.0)*
30.	2.0	—	(12.0)*
31.	0.2	0.3	(1.2)*

* Urinary excretion test using oral Co^{60}-B_{12} following two weeks of Aureomycin therapy.

The three patients with blind-loop syndrome showed markedly impaired absorption of oral vitamin B_{12} (urinary excretion, 0.2 to 2.6%). Retesting with intrinsic factor in one patient showed no change. Retesting following two weeks of therapy with chlortetracycline showed improved absorption in two cases, and no effect in the third (table 1, group C).

The majority of the patients were studied while in clinical and hematologic remission as a result of appropriate therapy, i.e., the defect in vitamin B_{12} absorption was present in the face of remission.

Discussion

Patients with sprue show a multiplicity of absorption defects. Of especial interest with regard to the hematologic abnormalities in sprue are difficulties in absorption of protein, folic acid, vitamin B_{12} and iron.[2] Difficulties in absorption as well as altered metabolism of protein may be responsible for the marked hypoproteinemia which is found in severe sprue.[8a] Experimentally, a deficient diet has further been shown to cause changes in the intestinal tract, with consequent impairment of absorptive functions.[9] The relationship of protein deficiency to the development of anemia has been documented in the experimental animal[10] and inferred in man;[11] and it has been suggested that, at least in part, the anemia is the result of a lack of protein supply to the marrow which causes a block in the normal development of the erythrocyte.[10] Protein deficiency at the sites of blood formation may be conjectured to contribute to the megaloblastic dyshematopoiesis which is the characteristic finding in malabsorption syndrome, just as it apparently does to the development of nutritional megaloblastic anemia.

Less speculative is the role played by deficiencies of folic acid and vitamin B_{12} at the bone marrow. It has been shown that patients with idiopathic steatorrhea regularly show impaired ability to absorb folic acid from the gastrointestinal tract, in contrast to normal individuals and to patients with pernicious anemia.[12] It has been abundantly demonstrated that most patients with idiopathic sprue will respond to the administration of folic acid with partial or complete clinical improvement.[13-17]

The intermediary metabolism of vitamin B_{12}, as well as that of folic acid, is incompletely understood. In the normal individual, vitamin B_{12} is absorbed from the small bowel following its interaction with a gastric material called "intrinsic factor." Absence of intrinsic factor leads to malabsorption of dietary vitamin B_{12} and, with depletion of the body stores of vitamin B_{12}, ultimately results in the picture of pernicious anemia.

Even in the presence of intrinsic factor, however, dietary vitamin B_{12} may fail of absorption, for other reasons. On the one hand, there is a group of disorders in which the ability of the small intestine to absorb vitamin B_{12} is impaired; this is the situation in the malabsorption syndrome. On the

other hand, an intraluminal parasite (*D. latum* infestation) or an altered intestinal flora (blind-loop syndrome) appears to prevent normal absorption of vitamin B_{12}, either by direct competition with the host for the vitamin, or perhaps by a "toxic" effect. In either case, elimination of the parasitic organism reverses the defective absorption of vitamin B_{12}.[18, 19]

According to these studies, patients with primary malabsorption may be divided into those in whom intestinal absorption of vitamin B_{12} in physiologic amounts is impaired (20 of our 25 cases), and those in whom such absorption is normal (five of our 25 cases). Others have similarly suggested, on other evidence, the existence of two types of primary sprue with regard to vitamin B_{12} metabolism. Thus, it has been shown that certain patients with sprue in relapse have abnormally low serum levels of vitamin B_{12}, whereas in others the levels are normal.[16, 20, 21] Further, it has been observed that certain patients with sprue respond to vitamin B_{12} alone,[20] whereas others respond to folic acid alone.[13-17] It may thus be assumed that

TABLE 2

Differentiation of Malabsorption of Vitamin B_{12}

	Vit. B_{12} Alone	Vit. B_{12} + I.F.*	Vit. B_{12} + Antibiotics
Normal	Normal	Unchanged	Unchanged
Pernicious anemia	Poor absorption	Improved	Poor absorption
Primary malabsorption syndrome	Poor absorption	Poor absorption	Poor absorption
"Blind-loop" syndrome	Poor absorption	Poor absorption	Improved

* I.F.—Intrinsic Factor.

the pathogenesis of the usual macrocytic megaloblastic anemia in patients with malabsorption syndrome varies in different patients. Thus, in some cases the predominant absorptive defect may be one of folic acid, in others of vitamin B_{12}; in still others, there may be a major disturbance in the absorption of both vitamins. A possible role of additional, as yet unidentified factors cannot be excluded. The role of genetically determined enzymatic mechanisms, possibly responsible for the absorption or utilization defect, must also be mentioned.[1]

It is important to emphasize that the test dose used to study absorption of vitamin B_{12} in this study was in the physiologic range, comparable to the amounts of the vitamin present in the normal diet. It is only at such dosage levels that vitamin B_{12} absorption is directly dependent upon intrinsic factor.[22] When larger amounts of vitamin B_{12} are given by mouth, intestinal absorption may occur without regard to this normal mechanism, apparently by a sort of "mass action" effect.[23] This has been demonstrated in patients with pernicious anemia; we have made similar observations in two patients with primary malabsorption syndrome (unpublished study).

The measurement of the intestinal absorption of vitamin B_{12} in physiologic doses as outlined in this and other reports [24-28] provides an additional technic in the study of the malabsorption syndrome. Our observations indicate that a defect in intestinal absorption of vitamin B_{12} is among the most consistent measurable abnormalities in the malabsorption syndrome. Radioactive vitamin B_{12} may be added to the tools employed in the diagnosis of this syndrome (table 2).

Summary

1. The intestinal absorption of vitamin B_{12} was measured by the urinary excretion of radioactivity following the oral ingestion of a physiologic dose of Co^{58} or Co^{60} labeled vitamin B_{12} in patients with primary and secondary malabsorption syndromes.

2. Absorption of vitamin B_{12} was impaired in 20 of 25 cases of primary malabsorption syndrome, in three cases of secondary malabsorption syndrome due to intestinal resection, and in three cases of blind-loop syndrome.

3. Absorption of vitamin B_{12} in these patients was not related to or improved by intrinsic factor.

4. As to intestinal absorption of vitamin B_{12}, patients with malabsorption states can be divided into several groups:

Primary malabsorption syndrome:

1. Impaired absorption of vitamin B_{12} (four-fifths of our patients).
2. Normal absorption of vitamin B_{12} (one-fifth of our patients).

Secondary malabsorption syndrome ("blind loop syndrome"):

1. Impaired absorption of vitamin B_{12}—not improved by antibiotics.
2. Impaired absorption of vitamin B_{12}—improved by antibiotics.

5. The significance of these findings in the pathogenesis of the characteristic hematologic abnormality of malabsorption syndrome is discussed.

Summario in Interlingua

1. Le absorption intestinal de vitamina B_{12} esseva mesurate per determinar le excretion urinari de radioactivitate post le ingestion oral de doses physiologic (0,4 a 0,5 μg) de vitamina B_{12} marcate per Co^{58} o Co^{60} in patientes con primari o secundari syndrome de malabsorption. Le technica usate esseva illo de Schilling.

2. Esseva constatate que le absorption intestinal de vitamina B_{12} esseva defective in 20 ex 25 casos (i.e. 80%) de syndrome de malabsorption primari, in tres casos de syndrome de malabsorption secundari a resection intestinal, e in tres casos de syndrome de ansa intestinal cec.

3. Le absorption intestinal de vitamina B_{12} in iste patientes non esseva relationate a factor intrinsec e non esseva meliorate per illo. In duo del tres patientes con syndrome de ansa cec, le absorption de vitamina B_{12} esseva meliorate post un curso de tractamento con chlortetracyclina.

4. Ab le puncto de vista del absorption intestinal de vitamina B_{12}, patientes con statos de malabsorption pote esser gruppate in plure categorias:

A. Syndrome de malabsorption primari.
   1. Absorption defective de vitamina B_{12} (quatro quintos de nostre patientes).
   2. Absorption normal de vitamina B_{12} (un quinto de nostre patientes).

B. Syndrome de malabsorption secundari.
   1. Absorption defective de vitamina B_{12}—non meliorate per antibioticos.
   2. Absorption defective de vitamina B_{12}—meliorate per antibioticos.

5. Vitamina B_{12} es un de plure substantias cuje malabsorption per le vias intestinal contribue al anormalitate hematologic characteristic del syndrome de malabsorption, i.e. anemia megaloblastic.

BIBLIOGRAPHY

1. Adlersberg, D.: Introduction to symposium on the malabsorption syndrome, J. Mt. Sinai Hosp. **24**: 177, 1957.
2. Estren, S.: The blood and bone marrow in idiopathic sprue, J. Mt. Sinai Hosp. **24**: 304, 1957.
3. Innes, E. M.: The blood and bone marrow in the sprue syndrome. A study of 63 cases, Edinburgh M. J. **55**: 282, 1948.
4. Bossak, E. T., Wang, C. I., and Adlersberg, D.: Clinical aspect of malabsorption syndrome, J. Mt. Sinai Hosp. **24**: 286, 1957.
5. Oxenhorn, S., Estren, S., and Adlersberg, D.: Intestinal uptake of vitamin B_{12} in the malabsorption syndrome, J. Mt. Sinai Hosp. **24**: 232, 1957.
6. Schilling, R. F.: Intrinsic factor studies. II. The effect of gastric juice on the urinary excretion of radioactivity after the oral administration of radioactive vitamin B_{12}, J. Lab. and Clin. Med. **42**: 860, 1953.
7. Callender, S. T., and Evans, J. R.: The biochemistry of vitamin B_{12}, 1955, Cambridge University Press, London, p. 68.
8. Lopez, G. G., Milanes, F., Spies, T. D., Toca, R. L., Aramburu, T., and Lopez, H.: The association of hypoproteinemia with severe tropical sprue, Am. J. M. Sc. **218**: 660, 1949.
   (a) Adlersberg, D., Wang, C., and Bossak, E.: Disturbances in protein and lipid metabolism in malabsorption syndrome, J. Mt. Sinai Hosp. **24**: 206, 1957.
9. Miller, D. K., and Rhoads, C. P.: The experimental production of loss of hematopoietic elements of the gastric section and of the liver in swine with achlorhydria and anemia, J. Clin. Investigation **14**: 153, 1935.
10. Aschkenasy, A.: On the pathogenesis of anemias and leukopenias induced by dietary protein deficiency, Am. J. Clin. Nutrition **5**: 14, 1957.
11. Fauvert, R., Hartmann, C., and Guénin, P.: Le retentissement hématologique des gastrectomies. L'anémie protéiprive. Etude de 110 cas de gastrectomies. Symposium sur les anémies dites de nutrition, Sang **23**: 745, 1952.
12. Girdwood, R. H.: A folic acid excretion test in the investigation of intestinal absorption, Lancet **1**: 53, 1953.
13. Cohen, B. S., Meyer, L. M., and Fadem, R.: Sprue refractory to vitamin B_{12}; satisfactory response to folic acid, Ann. Int. Med. **36**: 1533, 1952.
14. Israels, M. C. G., and Sharp, J.: Idiopathic steatorrhoea (non-tropical sprue) with megaloblastic anaemia, Lancet **1**: 752, 1950.
15. Tuck, I. M., and Whittaker, N.: Vitamin B_{12} in idiopathic steatorrhoea, Lancet **1**: 757, 1950.
16. Mollin, D. L., and Ross, G. I. M.: Serum vitamin B_{12} concentrations of patients with megaloblastic anaemia after treatment with vitamin B_{12}, folic acid, or folinic acid, Brit. M. J. **2**: 640, 1953.

17. Mueller, J. F., Hawkins, V. R., and Vilter, R. W.: Liver extract refractory megaloblastic anemia, Blood **4**: 1117, 1949.
18. Bjorkenheim, G.: Neurological changes in pernicious tapeworm anaemia, Acta med. Scandinav., Suppl. **260**: 1–124, 1951.
19. Halsted, J. A., Swendseid, M. E., Lewis, P. M., and Gasster, M.: Mechanisms involved in the development of vitamin B_{12} deficiency, Gastroenterology **30**: 21, 1956.
20. Mollin, D. L., and Ross, G. I. M.: Vitamin B_{12} deficiency in the megaloblastic anemias, Proc. Roy. Soc. Med. **47**: 428, 1954.
21. Meynell, M. S., Cooke, W. T., Cox, E. V., and Gaddie, R.: Serum cyanocobalamin level in chronic intestinal disorders, Lancet **1**: 901, 1957.
22. Booth, C. C., and Mollin, D. L.: Plasma, tissue and urinary radioactivity after oral administration of Co^{56} co-labelled vitamin B_{12}, Brit. J. Haematol. **2**: 223, 1956.
23. Ross, G. I. M., Mollin, D. L., Cox, E. V., and Ungley, C. C.: Hematologic responses and concentration of vitamin B_{12} in serum and urine following oral administration of vitamin B_{12} without intrinsic factor, Blood **9**: 473–488 (May) 1954.
24. Callender, S. T., and Evans, J. R.: Observations on the relationship of intrinsic factor to the absorption of labelled vitamin B_{12} from the intestine, Clin. Sc. **14**: 387, 1955.
25. Reisner, E. H., Jr., Gilbert, J. P., Rosenblum, C., and Morgan, M. C.: Applications of the urinary tracer test (of Schilling) as an index of vitamin B_{12} absorption, Am. J. Clin. Nutrition **4**: 134, 1956.
26. Glass, G. B. J.: Intestinal absorption and hepatic uptake of vitamin B_{12} in diseases of the gastrointestinal tract, Gastroenterology **30**: 37, 1956.
27. Krevans, J. R., Conley, C. L., and Sachs, M.: Influence of certain diseases on the absorption of vitamin B_{12} from the gastrointestinal tract, J. Clin. Investigation **33**: 949, 1954.
28. Best, W. R., White, W. F., Louis, J., and Limarzi, L. R.: Experiences with the Schilling test using Co^{60}-labelled vitamin B_{12} in pernicious anemia, sprue and other conditions, J. Lab. and Clin. Med. **44**: 767, 1954.

FURTHER OBSERVATIONS CONCERNING THE PROGNOSIS OF MYOCARDIAL INFARCTION DUE TO CORONARY THROMBOSIS*

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In 1926 one of us (P. D. W.) published the first of a series of papers on the prognosis of coronary heart disease as evidenced by coronary thrombosis or the symptom of angina pectoris based on the first group of those patients personally seen during the decade of 1921 to 1930, inclusive.[1] In 1931 a second paper was published,[2] this time by White and Bland, on the two series of patients seen in this decade, then amounting in numbers to 200 cases of coronary thrombosis and 500 cases of angina pectoris. In 1941 a third paper was published[3] by the same authors on a 10-year follow-up of the same series of 200 cases of coronary thrombosis. Finally, in 1956, a more or less final report was made of a 25 year follow-up of those same 200 cases by Richards, Bland and White.[4]

The principal and most important finding in our two latest reports was that, despite the extremely varied longevity of the total group after the onset of the first attack of coronary thrombosis with myocardial infarction, complete recovery of the patient a month or more after the acute lesion, with freedom from both myocardial and coronary insufficiency, presaged a good survival—that is, often for over 10 years—and a return to normal activity in the majority of cases. Incidentally, the two patients known to be living now, 29 or 30 years after infarction, are of the "complete recovery" group.

Following the publication of this paper, it was pointed out by one of us (S. A. L.) that it would be useful to analyze the cases further, with particular reference to the time after the onset of the acute illness at which they were seen in consultation, for it was obvious that the follow-up study reported did not represent the true prognosis of coronary thrombosis at its inception. This would permit a serial or selective prognosis according to time, although the number of cases in each group would necessarily be limited.

Thus, what happened to those cases first seen by P. D. W. during either the first week of their acute illness, or the second week, second fortnight or the second and third months, which would cover the duration of the process of infarction and of the immediate convalescence therefrom? It is obvious that the cases first seen after the first three months are of less importance prognostically, though still of some interest. Of the 200 cases originally

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reported, 56 were first seen during the first week, 11 more during the second week, 23 more during the second fortnight, and 32 others during the second and third months. It seemed to us that of special value would be the analysis of *the follow-up of the patients seen by P. D. W. during the first month who survived that first month.* It is that particular group of 55 cases which is emphasized in the present paper, although the entire group of the 122 cases seen during the first three months is of some—though much less—importance to the medical practitioner at large.

Not only are we herewith presenting this particular analysis, but we also wish to add further comments concerning the accuracy of any statistical data now available as to the prognosis of coronary thrombosis. The first of these concerns the prognosis at the very moment of its onset. Those individuals who have not previously sought medical advice for coronary heart disease and who die immediately, or within minutes or hours before they can be seen by any physician, fail to be tabulated clinically. Dr. Milton Helpern, coroner in New York City, who has had a rich experience in the postmortem examination of victims of sudden death, has estimated that about 25% of persons who so die, without being seen clinically at the time, show thrombosis of the coronary arteries. Whether this important omission from all current statistics can ever be properly corrected remains doubtful.

Second, it must be remembered that the decade from 1921 to 1930, inclusive, was at the very beginning of the general clinical recognition of coronary thrombosis, when it was viewed fatalistically, with pessimism (the mild cases being undiagnosed or "ruled out"); moreover, this was long before the days of anticoagulants.

A third consideration of much importance is that the cases reported in this series were seen by a consultant who was called in usually because of the severity of illness or because of doubt concerning the diagnosis. To get a more comprehensive clinical appraisal of the prognosis requires the long-term tabulation of data by the general practitioner, or family doctor, who sees the patient at the very beginning of his illness. Such data, so far as we know, do not exist at the present time, but efforts are under way to correct this difficulty. For example, at Grand Forks, North Dakota, during the current year, the physicians in the six northeastern counties of that State have banded together to report all their new cases of coronary thrombosis.

As stated in the early paper of 1931, the electrocardiogram did not at that time help in determining the gravity of the prognosis. In the first place, in the 1920's the electrocardiogram often was not taken, at least during the acute stage of the illness. (Actually, we have electrocardiograms of 127 of the 200 cases.) Second, only the routine three-limb leads were taken in those years. Third, subsequent experience has indicated the failure of the

electrocardiogram to enter very prominently into the prognosis, although a steadily worsening record during the first few months is an unfavorable sign.

Further Review of Data of Original Series of 200 Cases of Coronary Thrombosis

1. *Time of Examination of Patient When Seen in Consultation After Onset of the Acute Attack:*

A. *Within the first three months.* (That is, during the acute process and convalescence therefrom, 122 cases.) The mortality in this group was 34%. Forty-two cases out of the 122 died during the three months, the majority early during this period (26 * during the first two of the 13 weeks, and only 16 thereafter).

Table 1

Acute Cases of Myocardial Infarction, 1921–1930

Interval Between Attack and Consultation Within	Number of Cases		Deaths Within				
	Additional	Total	1 week	2 weeks	1 month	3 mos.	Total
6 hours		7	3	1	0	0	4
1–2 days	14	21	4	2	2	0	8
1 week	35	56	11	2	2	1	16
2 weeks	11	67	0	3	3	1	7
1 month	23	90	0	0	2	3	5
3 months	32	122	0	0	0	2	2
Total	122		18	8	9	7	42

a. *Within six hours:* Seven cases. Two died within a few hours, one lived three days, one nine days, one five years, one 12 years, and one 18 years.

b. *Within one to two days:* Fourteen more cases. One died the same day, one lived two days, one three days, one five days, two one week, two two to three weeks, one eight months, three lived one to two years, one lived nine years, and one 18 years.

c. *Within one week:* Thirty-five more cases, making a total of 56. Of the 35 additional cases, 15 died within the first month, one died in the second month, five more before the first year was up, and another five between the first and the fifth years; seven survived 10 years, and two more survived 25 years.

Another important question concerns the average duration of life and the complications that occurred in the 56 patients seen by P. D. W. within one week of the onset of their acute illness. Their duration of life from the onset of their attack ranged from a few hours to 30 years, with an average of 3.63 years; 29 of these 56 patients lived more than a month—that is, they

* Certainly many more than 26 would have died during the first 14 days if they had all been seen during the first hour or two of their first acute attack. Of the 56 who were seen during the first week, 23 died within 14 days. All 200 cases, however, as will be noted later, were severe (163 of the 200) or moderately severe (the remaining 37).

survived the acute attack. Of these, 14 (almost half) survived five years, of those 14 nine survived 10 years (slightly less than a third), three survived 15 years, and one survived 20 years and is still living 30 years following the attack. Complications occurring in these patients consisted of coronary insufficiency alone, as represented by either angina pectoris or sudden death in 19 cases; myocardial insufficiency alone, as represented by newly developing dyspnea in 10; both of these conditions together in five, shock in four, and hemiplegia in one. *Of the 17 (30%) who developed neither myocardial nor coronary insufficiency up to or close to the time of death, the average duration of life was 10.2 years, with a range of from one to 30 years; 13 survived five years, nine survived 10 years, four survived 15 years, and one, still alive, has survived 30 years.*

d. *Within one month:* Of the total of 90 * cases seen by P. D. W. within one month of the acute attack, 35 died during the month and 55 survived. Of the 35 who died, two lived only a few hours, six lived two to three days, eight lived four to five days, and two lived six to seven days, making a total of 18 during the first week. Eight died in the second week, and only nine more died in the last half of the month. All this, of course, points to a steadily and rapidly decreasing mortality during the first month after the acute attack, justifying a common practice of releasing patients from the "critical" or "danger" list after the first two or three weeks.

Of the 35 patients who died within the month, the average duration of life was 7.8 days, and the average time interval between the onset of their illness and examination by P. D. W. was 4.2 days, whereas of the 55 patients who survived, the average duration of life was seven years and three months, and the average time interval between the onset of their illness and examination by P. D. W. was 10.3 days.

Of the 55 survivors, 24 (or 44%) recovered completely, that is, with neither coronary nor myocardial insufficiency at the end of the first month. Of these 24, two lived over one but less than two years, two lived over two but less than three years (one of these was a suicide), two lived three to four years, three lived five to six years, two lived seven to eight years, two lived nine to 10 years, seven lived 10 to 15 years, two lived 15 to 20 years, and two survived 20 and 25 years, respectively. The average survival of 24 cases was just 12 years.

e. *During the second and third months,* 32 more patients were seen in consultation by P. D. W. Of these, two died and the other 30 survived three months.

B. The other 78 patients were seen after the first three months, 27 within the first year, 31 more within five years, the remaining 20 later. The average length of time between the onset of their illness and our examination

* This figure (previously recorded as 86) and several others to follow have been revised from those given in the papers published in 1941 [3] and 1956 [4] after a further detailed analysis of the individual case records.

was 30 months for the entire group of 78 patients, and their survival after the onset of their illness averages seven and a third years. Although these are consecutive cases seen by P. D. W., and they are all well authenticated instances of "first attacks," the fact that they were first seen months or years after the onset of the first attacks makes it impossible to regard them as *consecutive* cases of first attacks of myocardial infarction. Obviously if all the 200 cases had been seen during the first several days of their first attack, many would have died during the first few months and would not have seen a consultant for the first time two or three years later. There would, of course, have been a smaller percentage of the original survivors of the first attack who lived three, five, 10, 15, 20 years or more after the first attack.

This group of 78 patients does, to be sure, contain a considerable number of the long survivors (24 over 10 years), who are, however, also very well represented (24 over 10 years) in the first group of the 122 cases seen during the first three months.

Another special question concerned the average time interval between the onset of the illness and examination by P. D. W. in the series of 122 cases seen during the thrombosis and the immediate convalescent period. On calculation, this proved to be approximately three weeks (22.5 days). Of the 90 cases seen during the first month, the time interval averaged eight days between the onset of the illness and examination by P. D. W.

2. *Comparison of Patients Who Survived the First Month but Who Died Within Three Years With Those Who Survived Five Years:* This comparison seemed of particular interest and value from the standpoint of prognosis. We have included in this comparison only the cases seen by P. D. W. within a month of the onset of their attack. There were 25 cases in the former group and 23 in the latter; the remaining seven patients died in the fourth and fifth years after the attack.

A. Of the 25 survivors of the first month who died within three years, 14 (over half) of the 25 patients had congestive failure, and several (six) of these 14 had coronary insufficiency also. Seven other cases had coronary insufficiency without congestive failure. Only four (16%) of the 25 patients who died within three years had recovered completely from the initial episode, that is, having neither myocardial nor coronary insufficiency; of these four, one had later attacks of coronary thrombosis, one died suddenly (probably of coronary insufficiency), one developed angina pectoris later and died in congestive failure, and the fourth committed suicide.

B. Of the 23 patients who survived five years, only one had congestive failure on recovery from the acute attack (accompanied by angina pectoris). However, four other patients who had angina pectoris following the attack survived the five years despite it although all of them eventually did die of coronary insufficiency (two) or recurrent attacks of coronary thrombosis (two). On the other hand, 18 of these 23 five-year survivors showed neither coronary nor myocardial insufficiency after the attack (78%, in

contrast to only 16% of those who survived the first month but did not survive three years).

C. Of the seven patients who died in the fourth and fifth years after the attack, three had both myocardial and coronary insufficiency on survival from the acute attack, two had angina pectoris only, and two had neither.

D. Thus, this state of complete recovery appears to be the most favorable prognostic clue of all for those who weathered the attack itself. This will be presented in more detail in the next paragraphs.

3. *A Comparison Has Been Made of the Effects of the Three Most Important Clues at the End of the First Month After the Attack on the Long Range Prognosis:* These clues are worthy of special mention because of their great significance. They are (a) dyspnea due to left ventricular failure, (b) angina pectoris due to coronary insufficiency, and (c) complete recovery with neither myocardial nor coronary insufficiency. Reference has been made above to these clues in both the 1941 and the 1956 papers, but they are so important that they deserve more detailed review and renewed emphasis.

(A) *Left ventricular failure:* Eighteen (33%) of the 55 patients who were seen during the first month and who survived that first month after the onset of coronary thrombosis were limited by dyspnea; half of these patients (nine) also had coronary insufficiency. There were, in addition, 11 other patients who succumbed to myocardial failure during the first month. Of the 18 patients with dyspnea who survived the first month, 12 (two thirds) died within a year, and five more within five years; only one survived five years. This complication, therefore, is serious and shortens life.

(B) *Coronary insufficiency:* Of 13 cases (24% of the 55 patients who were seen by P. D. W. during the first month and survived) without myocardial insufficiency but limited by angina pectoris after recovering from the first attack of myocardial infarction, four (31%) died within a year, five more (38%) died within five years, four (31%) survived five years, three (23%) survived 10 years, one survived 15 years, but none survived 20 years. Thus this complication is considerably less serious than myocardial failure.

(C) *Complete recovery:* Finally we come to the 24 patients (44% of the 55 survivors) who showed neither myocardial nor coronary insufficiency one month after recovering from their acute attack. This is, as would be expected, the most favorable group. None died within a year of the onset of their attacks; only four (17%) died within three years; two (8%) died during the fourth and fifth years after the attack, *while 18 (75%) survived five years;* 11 (46%) survived 10 years; four (17%) survived 15 years, and two (8%) survived not only 20 but also 25 years. The longest survivor of the total group of 55 patients, by 30 years, belongs in this most favorable group.

4. Another important question concerns the *causes of death among the completely recovered cases,* of whom there were 61, including the six who lived less than three years, the four who died in the fourth and fifth years after their attack, and the 51 who survived five years. This group includes, of course, the 24 completely recovered cases who, as just noted, were seen by P. D. W. during the first month of their acute illness. They were as listed in table 2.

5. *The Severity of the Attack.* On careful analysis of the severity of the attack, it was quickly and clearly evident that there were no mild cases. Either such were not being diagnosed during that decade, or P. D. W. was not asked to see them in consultation. Both are likely. This failure to include any mild cases may well explain the high mortality (34%) in the

TABLE 2

Eventual Causes of Death in the "Completely Recovered" Cases

Recurrent attacks of coronary thrombosis		21
Second attack	14	
Third attack	2	
Fourth attack	4	
Fifth attack	1	
Sudden death (doubtless due to coronary insufficiency):		
5 had developed angina pectoris		14
Total coronary deaths		35
Unknown cause (doubtless several were "coronary")		10
Cancer		4
Cerebral vascular accidents with hemiplegia		3
Suicide		1
Pulmonary embolism		1
Miscellaneous		7
Total		61

group of 122 patients seen during the illness and convalescence of their first attack of coronary thrombosis. Actually, of the total number of 200 cases, 163 were severe and the remaining 37 moderate in degree.

6. *Adequacy of Treatment and Coöperation of Patients:* Treatment and patients' coöperation were often difficult to appraise from a review of the records or from memory, but now and then these were clearly defined. At least 35 of the 200 were either uncoöperative or, more likely, did not understand the treatment advised, we doctors in those days not always having made it clear that complete rest was essential during the first few weeks. One patient, taken sick in another city, took the train to Boston the next day—not the best therapy; another, not yet under nursing care, arose the morning after to take a tub bath and to shave after it, happily without difficulty. A few patients, believing that their lives would be short at best, probably shortened them further by ignoring all medical advice and carrying on full activity. Great improvement both in treatment and in coöperation

of patients doubtless helps to account for a better prognosis now than occurred in the group in the 1920's.

7. Family History: There was little to be learned about family history from the records, which until 1926 were woefully inadequate, with simple notations such as "negative," "good," "very good," "long-lived," "poor" or "————." Apparently in or about 1926 P. D. W. began to regard the family history seriously, noting the age and cause of death in father, mother and siblings, but there was still no statement about grandparents, whose longevity was not recognized as important until a decade or two later. From the records of the 200 cases there was little information of value in this respect. Of 55 patients who died within five years, both parents had survived 70 years in 19 cases, and both had died before the age of 60 years in nine. Of 32 patients who lived more than five years, both parents had survived 70 years in eight instances, while both had died before the age of 60 in three. The cause of death was rarely stated. Much more information (although still less than adequate) was presented in the following decade and has been recorded since then.

In 1931 Musser and Barton [5] read a paper before the American Heart Association at Philadelphia entitled "The Familial Tendency of Coronary Disease," quoting a number of earlier authors who, like themselves, recorded individual families afflicted with coronary heart disease but gave no general statistics.

In 1934 Eppinger and Levine [6] made a study of the ages at death of two groups of patients with angina pectoris. In the first group the parents had lived to an average age of over 70; 26 patients who comprised this group averaged 63.4 years at death. In the second group the average age of the parents at death was under 60 (52.1 years), and in that group 19 patients died at the average age of 57.8 years. Those patients with angina pectoris who had long-lived ancestors lived 5.6 years longer than those whose parents had died at an earlier age.

In a study of 300 individuals who had coronary thrombosis, Goldsmith and Willius [7] reported in 1937 that there was a family history of cardiovascular renal disease in 165 cases (14 with coronary thrombosis).

Gertler and White [8] have reported an increased incidence of coronary heart disease in the families of young adults who have had myocardial infarction. Ninety-seven males who had had myocardial infarction were compared with 146 male controls. Forty-five per cent of the parents of the coronary group were alive at the time of our examination of these young adults, in contrast to 50% of the parents of the control group of the same ages alive at that time. Fifty-one per cent of the deceased mothers in the patient group had died of cardiovascular disorders (of all kinds), as compared with 35.9% in the control group, while 64.6% of the deceased fathers in the patient group had died of cardiovascular defects, as compared with 46.2% in the control group. The patients' fathers showed a larger pro-

portion of deaths due to disease of the coronary arteries—37.1% compared to 18.5%—a significant difference, although the mothers did not show such a difference (9.8% in the coronary group and 7.8% in the control group). Finally, among the siblings, five of 58 deceased siblings of the coronary patients had died from coronary heart disease, as compared with only one out of 98 in the control group.

Summary and Conclusions

1. A further analysis of 200 cases of coronary thrombosis with myocardial infarction seen in consultation between 1921 and 1930, inclusive, has shown that seven were examined within six hours, 14 more within two days, and 35 more within the first week, making a total of 56 during the first week. During the next three weeks, 34 more were seen, or a total of 90 in the first month. Thirty-two others were seen in the next two months, making a total of 122 patients seen during the acute attack and convalescence therefrom. The remaining 78 patients were seen in consultation later than that.

2. It is of much interest that there was a steadily decreasing mortality during the first three months. Of 35 who died in the first month, 18 died in the first week and eight in the second week. Of the 42 who died in the first three months, 26 succumbed in the first fortnight, nine more in the second fortnight, and only seven others in the second and third months. It should also be noted that coronary thrombosis kills a certain, at present indeterminable number of patients too quickly for them to be included in any clinical series.

3. A comparison of the 25 patients among the 90 who were seen by P. D. W. during the first month of their illness and who survived that month and yet died within three years of the onset of their attacks with 23 of this same group of 90 who survived five years showed that, among the former, 14 had congestive heart failure (six had coronary insufficiency also), seven had angina pectoris without congestive failure, and only four were free from evidence of either complication during their convalescence after the first month; among the latter 23 (who survived five years), only one had congestive failure, four others had angina pectoris, and 18 had recovered completely from their acute attack, showing neither complication.

4. As emphasized in the 1941 and 1956 reports, the most important clue favoring longevity and a return to a normal program of life was found to be the degree of completeness of recovery after the first month of convalescence from the acute attack. Of the 24 cases who showed neither myocardial nor coronary insufficiency, 18 (75%) survived five years, while the average survival of these 24 cases was 12 years.

5. Among those who, free of complications, completely recovered from their attack, the eventual cause of death was most commonly coronary, either

recurrent thrombosis or sudden death, with or without evident angina pectoris.

6. There were no mild cases in the whole group of 200 patients, either because such cases were missed or because a consultant was not called in to see such patients. There were 163 of severe and 37 of moderate grade.

7. Not infrequently during the 1920's the treatment and coöperation of patients such as those seen then by P. D. W. in consultation were inadequate.

8. It should be added that our attitude concerning the prognosis of coronary thrombosis with myocardial infarction will undoubtedly be much more optimistic in the future than it has been in the past because of the recognition of mild cases, the better treatment and program after recovery, and the more satisfactory understanding and coöperation of the patient.

SUMMARIO IN INTERLINGUA

1. Un analyse additional de 200 casos de thrombose coronari con infarcimento myocardial vidite al consultation inter 1921 e le fin de 1930 ha monstrate que septe esseva examinate intra sex horas, septe plus dece-quatro intra duo dies, e septe plus dece-quatro plus trenta-cinque intra le prime septimana. Assi le total pro le prime septimana esseva 56. In le curso del sequente tres septimanas, 34 casos additional esseva vidite, de maniera que le total pro le prime mense esseva 90. Trenta-duo casos esseva vidite in le curso del sequente duo menses. Isto significa que 122 patientes esseva vidite durante le attacco acute o durante le convalescentia ab illo. Le remanente 78 patientes esseva vidite in consultation a un tempore plus tardive.

2. Es multo interessante notar que le mortalitate declinava continuemente durante le prime tres menses. Inter 35 mortes durante le prime mense, 18 occurreva durante le prime septimana e octo durante le secunde. Inter le 42 mortes durante le prime tres menses, 26 occurreva durante le prime dece-cinquena, nove alteres durante le secunde, e solmente septe alteres durante le secunde e le tertie mense. Es etiam a notar que in un certe non nunc determinabile numero de casos, le morte del patientes con thrombose coronari occurre si rapidemente que nulle serie clinic pote includer lo.

3. Un comparation del 25 patientes qui (1) esseva inter le 90 vidite per Paul Dudley White durante le prime mense de lor morbo, (2) superviveva ille mense, sed (3) moriva intra tres annos post le declaration de lor attaccos con le 23 qui (1) pertineva al mesme gruppo de 90 patientes e (2) superviveva cinque annos monstrava que le prime serie, i.e. le serie de 25 patientes, includeva 14 qui habeva congestive disfallimento cardiac (in sex casos in association con insufficientia coronari), septe qui habeva angina de pectore sin disfallimento congestive, e solmente quatro qui non exhibiva signos de tal complicationes durante lor convalescentia post le prime mense, durante que le secunde serie, ille de 23 patientes, includeva un sol qui habeva disfallimento congestive, quatro alteres qui habeva angina de pectore, e 18 qui se restabliva completemente ab lor attacco acute e monstrava nulle del mentionate complicationes.

4. Como le reportos de 1941 e 1956 lo sublineava, le plus importante augurio in favor de longevitate e de retorno a un normal programma de activitates esseva trovate in le grado de completion del restablimento post le prime mense de convalescentia ab le attacco acute. *Inter le 24 patientes sin signos de insufficientia myocardial o coronari, 18 (i.e. 75%) superviveva cinque annos, e le superviventia medie pro iste integre gruppo de 24 patientes esseva 12 annos.*

5. Inter le patientes qui se restabliva completemente ab lor attaccos e esseva libere de complicationes, le causa le plus commun del morte subsequente esseva de

natura coronari. Le morte esseva causate per recurrentia de thrombose o occurreva subitemente con o sin evidente angina de pectore.

6. Nulle leve casos esseva includite in le serie total de 200 patientes. Iste facto ha duo explicationes possibile: (1) Tal casos non esseva recognoscite correctemente o (2) in illos nulle consulente esseva invitate a examinar le patiente. Le serie consisteva de 163 casos de grado sever e de 37 casos de grado moderate.

7. In le decennio post 1920, il non esseva infrequente que le tractamento e etiam le cooperation de patientes, como illes vidite per Paul Dudley White in consultation, esseva inadequate.

8. Il es necessari adder que nostre attitude con respecto al prognose de thrombose coronari con infarcimento myocardial va sin dubita esser plus optimistic in le futuro que illo esseva in le passato. Le justification de iste expectation es (1) le recognition de leve casos, (2) le melioration del tractamento e del regime post-therapeutic, e (3) le plus satisfacente comprension e cooperation del parte del patiente.

BIBLIOGRAPHY

1. White, P. D.: The prognosis of angina pectoris and of coronary thrombosis, J. A. M. A. **87**: 1525, 1926.
2. White, P. D., and Bland, E. F.: A further report on the prognosis of angina pectoris and of coronary thrombosis. A study of five hundred cases of the former condition, Am. Heart J. **7**: 1, 1931.
3. Bland, E. F., and White, P. D.: Coronary thrombosis (with myocardial infarction) ten years later, J. A. M. A. **117**: 1171, 1941.
4. Richards, D. W., Bland, E. F., and White, P. D.: A completed twenty-five-year follow-up study of 200 patients with myocardial infarction, J. Chron. Dis. **4**: 415 (Oct.) 1956.
5. Musser, J. H., and Barton, J. C.: Family tendency of coronary disease, Am. Heart J. **7**: 45, 1931.
6. Eppinger, E. C., and Levine, S. A.: Angina pectoris: some clinical considerations, with especial reference to prognosis, Arch. Int. Med. **53**: 120, 1934.
7. Goldsmith, G. A., and Willius, F. A.: Bodily build and heredity in coronary thrombosis, Ann. Int. Med. **10**: 1181, 1936–37.
8. Gertler, M. M., and White, P. D., with the aid, advice, and assistance of Bland, E. F., Fertig, J., Garn, S. M., Lerman, J., Levine, S. A., Sprague, H. B., and Turner, N. C.: Coronary heart disease in young adults, 1954, Harvard University Press, Cambridge.

HYPOVENTILATION SYNDROME: PHYSIOLOGIC STUDIES IN SELECTED CASES*

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Hypoventilation of the lungs, leading to lowered arterial oxygen saturation, carbon dioxide retention and respiratory acidosis, has long been recognized as a prominent feature of diffuse obstructive emphysema. Less well appreciated is the fact that significant hypoventilation may occur in other conditions both with and without obvious evidence of pulmonary disease. Prompt recognition of this situation is essential, since further reduction of ventilation, such as may result from the use of narcotics, or injudicious treatment with oxygen, may produce serious consequences. In addition, mental symptoms, presumably related to carbon dioxide retention, may develop in these individuals. These are particularly important because of their potential reversibility, and because their cause may be entirely unsuspected.

Some of the problems encountered in these individuals are illustrated by observations made in the following four cases, drawn from studies in a larger group in whom hypoventilation had been anticipated. Pulmonary function studies were performed as follows: Lung volumes and maximal breathing capacities were measured with a Benedict-Roth respirometer with the directional valves removed. Ventilation per minute and respiratory depth and frequency were obtained in an open circuit system, employing a Douglas bag for the inspired gas and a Tissot spirometer for the expired gas, measurements being made during the last five minutes of a 15-minute breathing period. Per cent of O_2 and CO_2 in expired air was determined by the Scholander technic.[1] Arterial blood specimens were drawn during the last minute of the ventilation measurement, and analyzed for O_2 content and capacity, and CO_2 content in the Van Slyke manometric apparatus.[2] Arterial O_2 and CO_2 tensions were performed by the Riley bubble method, as modified by Brinkman et al.,[3] and checked against the Singer-Hastings nomogram.[4] Arterial pH was measured at 38° C. in a water-jacketed Cambridge glass electrode. Physiologic dead space and alveolar ventilation were calculated from the Bohr equation,[5] assuming the arterial CO_2 tension to be equal to mean alveolar CO_2 tension.

Findings in the first case represent the prototype of the physiologic abnormalities encountered in association with a severe mechanical impairment

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of ventilation. The patient's mental symptoms and the reversibility of the pulmonary insufficiency make the case of unusual interest.

Case Reports

Case 1. A 43 year male auto designer developed kyphoscoliosis at age eight as a result of poliomyelitis. At age 42 he consulted his physician because of fatigability, lightheadedness, difficulty with concentration and spells of drowsiness, complaints which had been severe enough to interfere with his normal work. During the following year he was seen by a psychiatrist and a neurologist, in addition to his family physician, without a definite diagnosis being made. The existence of severe pulmonary insufficiency with carbon dioxide retention was unsuspected until the patient was admitted to the hospital with an acute respiratory infection, and became confused and stuporous when 100% oxygen was administered by mask. With the cessation of oxygen he again became responsive and lucid, although quite cyanotic, a

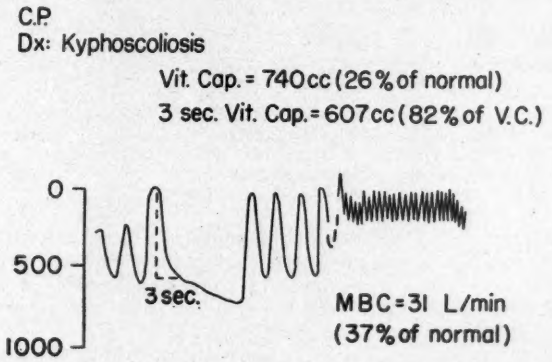

Fig. 1. *Case 1.* Spirogram, showing marked restrictive impairment of ventilation.

situation observed previously in patients with advanced pulmonary emphysema.[6, 7] Examination and laboratory studies indicated the presence of congestive heart failure and cor pulmonale secondary to a marked mechanical restriction of ventilation, as illustrated by the spirogram performed some time later (figure 1).

Arterial blood studies confirmed the existence of pulmonary insufficiency (figure 2), characterized by a marked fall in arterial oxygen saturation to 36%, a greatly elevated carbon dioxide tension (77 mm. Hg), and a low arterial pH, indicating a respiratory acidosis. Response to inhalation of 100% oxygen was dramatic, producing a marked reduction in ventilation, stupor, and aggravation of the arterial blood abnormalities. With the use of 30% oxygen, reduction of ventilation was less, but much the same arterial blood response was obtained.

Considerable improvement was obtained after vigorous treatment for congestive failure and respiratory infection, but it could not be maintained without the use of supplemental oxygen therapy. Consequently, a program of prolonged low-flow oxygen therapy was initiated, using a nasal catheter with two openings which fitted just inside the nostrils, and a small portable oxygen tank. After approximately six weeks of this program, with oxygen used continuously at night and during most of the day, arterial blood analyses (figure 3) revealed only mild arterial oxygen unsaturation, much less elevation of carbon dioxide tension, and a restoration of blood pH to normal

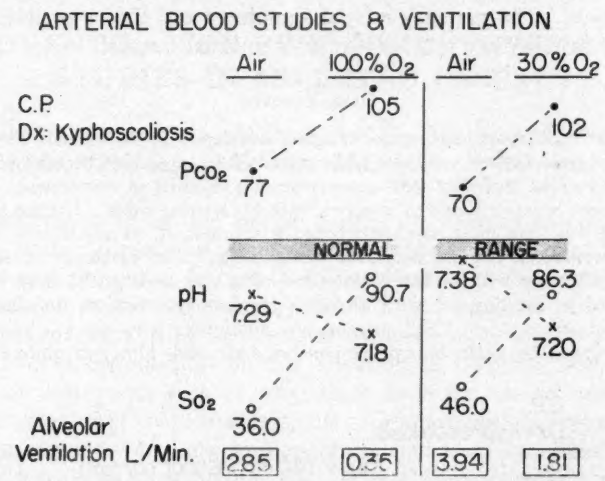

FIG. 2. *Case 1.* Response to inhalation of 100% and 30% O_2, showing rise in carbon dioxide tension and fall in pH accompanying marked reduction in alveolar ventilation in each case. (N.B. Alveolar ventilation figures here and in figure 8, Case 3, where predicted instead of measured dead space was used, may be lower than actual values.[17] Symbols: P_{CO_2} = carbon dioxide tension, mm. Hg; $S_{O_2} = O_2$ saturation, %.

by a compensatory rise in bicarbonate. Administration of both 30% and 100% oxygen now resulted in no change in arterial carbon dioxide tension or pH, indicating that ventilation was no longer depressed by oxygen inhalation. A surprising rehabilitation of this individual has been achieved; he is back at work full time and his mental symptoms have cleared completely.

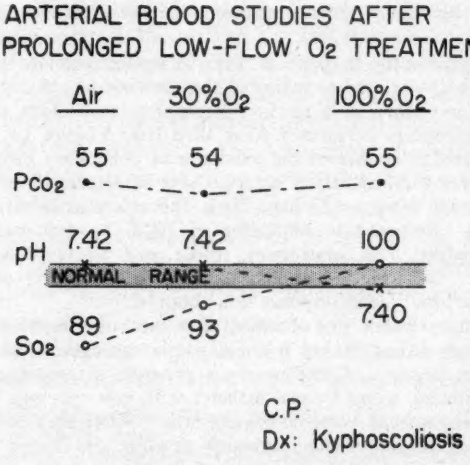

FIG. 3. *Case 1.* Status after therapy; no change in carbon dioxide tension and pH during inhalation of 30% O_2 and 100% O_2, respectively.

The next two cases illustrate two different types of mechanical restriction of the thorax, leading to difficulty with hypoventilation. The first of these demonstrates clearly the hazard of narcotic administration to these individuals.

Case 2. A man, age 45, had developed bilateral pleural effusion and signs of pericarditis six years previously. A diagnosis of tuberculosis was made, although only one positive culture was ever obtained, and the patient was treated with prolonged antituberculous chemotherapy. After a period of apparent good health, re-

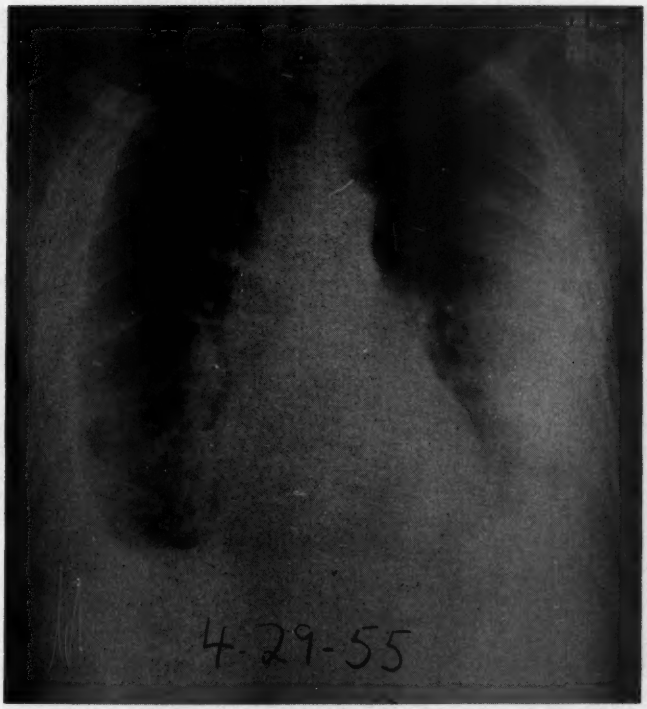

FIG. 4. *Case 2.* Chest film prior to decortication, showing bilateral pleural effusion.

curring effusion and signs of constrictive pericarditis developed. His chest film at that time is shown in figure 4. A left decortication and pericardiectomy were performed and tolerated well, with apparent clinical improvement. Ventilatory studies performed three months after this operation exhibited a characteristic picture of restrictive impairment of ventilation (figure 5). Five months after the first operation, right decortication was undertaken. On the second postoperative day, shortly after the injection of 10 mg. of morphine sulfate, pallor, drowsiness and shallow respirations were noted and the patient was placed in an oxygen tent. Further respiratory depression and stupor ensued, followed by the picture of shock. Fortunately, the condition was recognized as an acute respiratory depression, and good response was obtained from the administration of N-allylnormorphine and withdrawal of

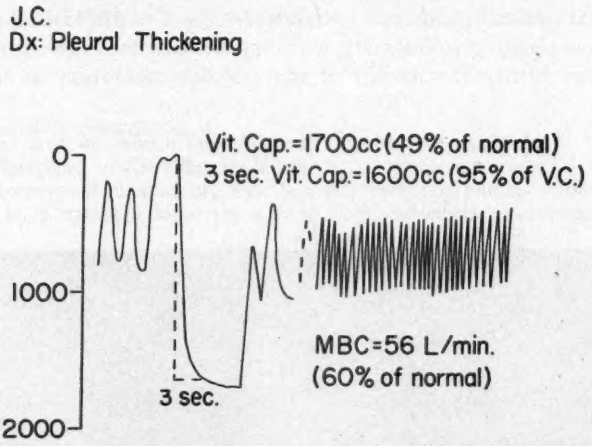

FIG. 5. *Case 2.* Spirogram of left lung, five months after decortication, showing restrictive impairment of ventilation.

oxygen. From that time on, however, the patient continued to demonstrate signs of pulmonary insufficiency and intermittent congestive heart failure. Ventilation and arterial blood studies performed at different times during his course exhibited the picture of respiratory failure, primarily due to impaired ventilation (figure 6). Response to oxygen inhalation was striking: even a relatively small increase in inspired oxygen produced a significant reduction of ventilation, although 100% saturation of the blood was easily achieved. This effect was invariably accompanied by drowsiness and sometimes stupor. Although temporary benefit was obtained with

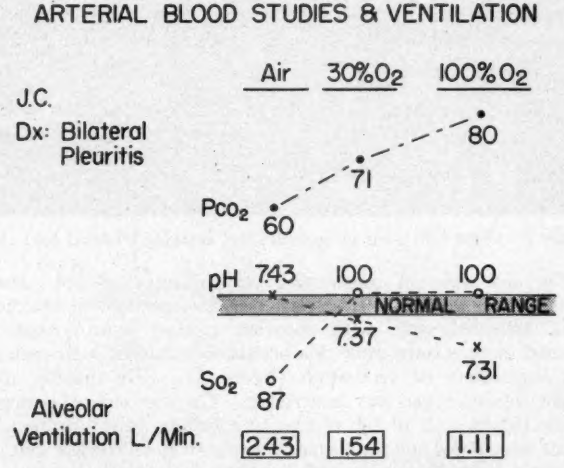

FIG. 6. *Case 2.* Response to inhalation of 30% and 100% O_2, respectively, showing reduced alveolar ventilation, lowered pH and rise in carbon dioxide tension in both instances. (Symbols as in figure 1.)

the use of intermittent positive pressure breathing and a mechanical respirator, the patient went gradually downward and died a year and a half after his second operation.

A third type of mechanical hypoventilation remained undetected until four weeks before the death of the patient.

Case 3. This 54 year woman had had pulmonary tuberculosis involving the right upper lobe 18 years before. During that illness a right phrenic crush had been performed, apparently resulting in a permanently paralyzed right hemidiaphragm.

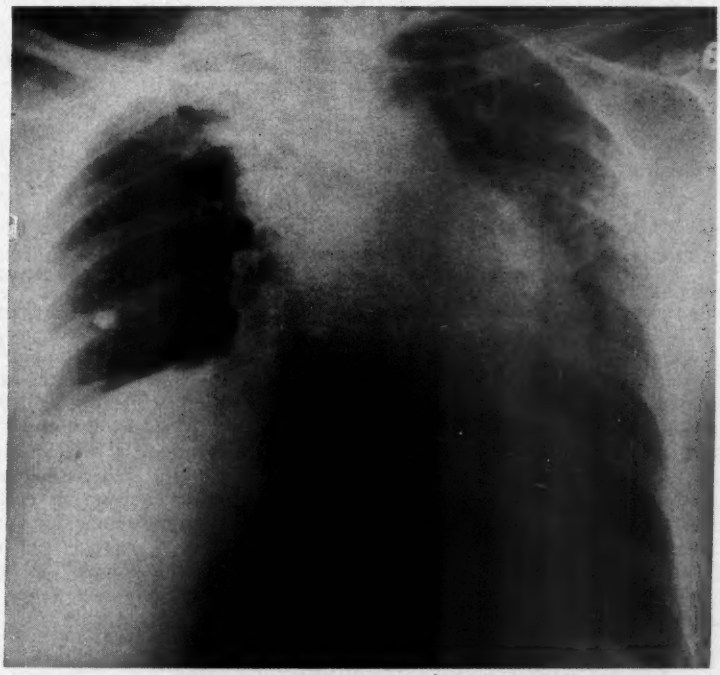

FIG. 7. *Case 3.* Chest film, showing radiation fibrosis and contracted left lung; old pulmonary tuberculosis with paralyzed hemidiaphragm on the right.

Six years before admission a left radical mastectomy had been performed for carcinoma of the breast, followed by an undetermined amount of radiation over the left thorax. The present admission was precipitated by the development of a respiratory infection, followed by marked exertional dyspnea and ankle swelling. On examination, deep cyanosis was apparent, as well as dyspnea and extensive edema of the legs. Chest film (figure 7) demonstrated a high right diaphragm, old pulmonary tuberculosis in the right upper lobe, and fibrosis and contracted lung on the left. Some improvement occurred after vigorous treatment on a cardiac program, but confusion and somnolence were noted during therapy with nasal oxygen at 4 L./min. flow, although visible cyanosis completely disappeared. Arterial blood and ventilation studies (figure 8) done one week after admission disclosed pulmonary insufficiency accompanying a marked hypoventilation state.

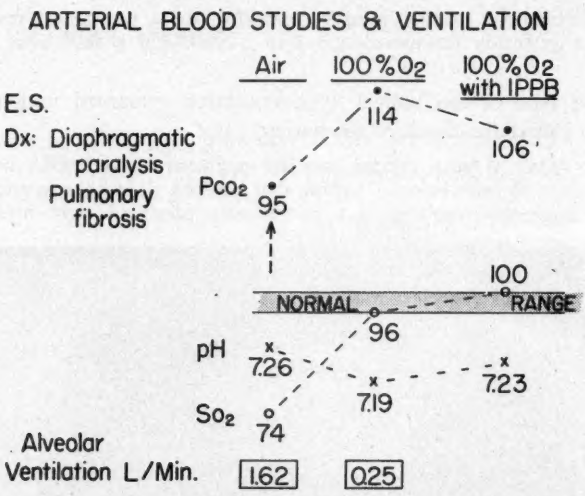

FIG. 8. *Case 3.* Response to inhalation of 100% O_2, and 100% O_2 with intermittent positive pressure breathing; marked alveolar hypoventilation (see note, figure 1), and respiratory acidosis, with little change after 15 min. of IPPB. (Symbols as in figure 1.)

Alveolar ventilation was measured at the very low level of 1.62 L./min. Accompanying this was a low oxygen saturation of 74%, a severe elevation of carbon dioxide tension to 95 mm. Hg (normal, 38 to 42), and a low pH of 7.26. After the patient had breathed 100% oxygen an almost normal oxygen saturation was obtained, but at the expense of a further reduction in ventilation, and consequent increase in carbon dioxide retention, and respiratory acidosis. Fifteen minutes of intermittent positive pressure breathing with 100% oxygen resulted in complete oxygen saturation of the arterial blood but only a slight fall in carbon dioxide tension.

Therapy was attempted with a rocking bed in an effort to improve ventilation, but it was unsuccessful because the patient's respiratory efforts could not be coordinated with the motion of the bed. She died rather abruptly two weeks after admission.

The last patient exhibits many characteristics of the so-called "Pickwickian" syndrome, a type of cardiopulmonary failure associated with gross obesity, as described in several recent case reports.[8-12] Although hypoventilation appears to be the basic defect in these individuals, its mechanism may involve an abnormal response of the respiratory center to the carbon dioxide stimulus.

Case 4. The patient was a 51 year woman, 5 feet 1 inch tall and weighing 220 pounds, with complaints of swelling of her legs and marked drowsiness and somnolence. She frequently fell asleep while sitting on the toilet, occasionally in the midst of a conversation, and once while counting cash receipts at home. A chronic wheezy cough had been present intermittently for years, and she was a heavy smoker.

Ventilation and arterial blood studies (figure 9) showed the abnormalities associated with hypoventilation, namely: (1) a considerable decrease in alveolar ventilation, a low arterial oxygen saturation, and an increase in carbon dioxide tension

while breathing air; (2) the reverse of the normal response when breathing 100% oxygen, namely, a further increase in carbon dioxide tension and a slight fall in pH, in spite of good oxygenation, a picture characteristic of alveolar hypoventilation.

Discussion

Individuals who might be expected to exhibit the hypoventilation syndrome fall into two main categories: those with mechanical restriction of the bellows, such as may occur in bony deformities of the thorax, pleural symphysis, and affections of the muscles or nerves of respiration; and those with primary depression of the respiratory center by drugs, anesthesia or disease. Under certain circumstances, such as immediately following a laparotomy [13, 14] and in gross obesity, both mechanical factors and central nervous system depression may play a part in the production of hypoventilation.

The fact that pulmonary function studies show relatively little abnormality in the majority of individuals in whom hypoventilation might be expected indicates that a critical point must be reached in order to produce decompensation, just as is the case with other organs of the body. It is significant that congestive heart failure was present in three of the four patients here presented. Studies in mitral stenosis suggest that the work of breathing is increased [15] and the respiratory response to carbon dioxide decreased [16] in this condition. Much the same situation might be expected in the congested lung of chronic cardiac failure associated with cor pulmonale; if this is the case, both factors would be expected to contribute to significant hypoventilation.

From the practical standpoint, the depth of respiration should serve as the most important guide to ventilation. In particular, the clinician must

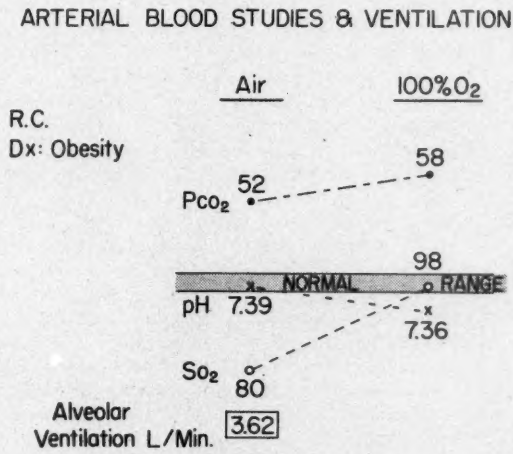

Fig. 9. *Case 4.* Respiratory acidosis, slightly increased by inhalation of 100% O_2.

not be misled by good oxygenation of the patient under oxygen therapy, a situation which may be accompanied by severe hypoventilation and respiratory acidosis. Should significant hypoventilation be detected, high concentrations of oxygen should be avoided, narcotics administered only with extreme caution, early tracheotomy considered for reduction of dead space and removal of secretions, and mechanical aids to respiration, such as intermittent positive pressure breathing, respirators and rocking-beds, given a thorough trial.

Summary

1. Hypoventilation of the lungs leading to pulmonary insufficiency and respiratory acidosis may be present in a variety of conditions which either mechanically restrict thoracic motion or depress the respiratory center.

2. Arterial blood and ventilation studies in four patients with diagnoses of kyphoscoliosis, bilateral pleuritis, radiation fibrosis and gross obesity, respectively, are presented.

3. All four patients demonstrated varying degrees of alveolar hypoventilation, accompanied by low arterial oxygen saturation, elevated carbon dioxide tension and low pH.

4. Administration of 100% oxygen resulted in reduction of ventilation in all, and symptoms of confusion and stupor in three.

5. Respiratory depth is the best practical guide to adequacy of ventilation.

6. In the presence of hypoventilation, caution is necessary in the use of high concentrations of oxygen and in the administration of narcotics. Therapy with mechanical aids to respiration should be tried, and tracheotomy used early when indicated.

Summario in Interlingua

Le presentia de hypoventilation del pulmones (reducite ventilation alveolar) con concomitante retention de CO_2 e acidosis respiratori es hodie un ben-recognoscite phenomeno in chronic emphysema pulmonar e sever asthma bronchial. Minus ben appreciate es le occurrentia de iste phenomeno in altere conditiones con o sin obvie morbo pulmonar, como per exemplo in cyphoscoliosis sever, morbo pleural extense, invenenamento per barbituratos, e grados pronunciate de obesitate e etiam post major interventiones chirurgic.

Es presentate quatro casos de iste syndrome. Le diagnoses in illos esseva (1) cyphoscoliosis sever, (2) fibrosante pleuritis bilateral, (3) fibrosis radiational e paralyse del hemidiaphragma, e (4) obesitate grossier. Studios del function pulmonar in iste individuos demonstrava reduction del saturation oxygenic arterial, elevation del tension de CO_2 arterial, e usualmente un reducite pH arterial insimul con defectivitate ventilatori. Esseva monstrate que iste anormalitates esseva associate con marcate grados de hypoventilation alveolar. Le administration de 100% de oxygeno a iste individuos resultava invariabilemente in un reduction additional del ventilation alveolar con augmento del tension de CO_2 arterial in despecto de bon oxygenation. In le presentia de congestive insufficientia cardiac, mesmo un leve augmento del oxygeno in le aere inspirate (30% de O_2) resulta usualmente in un reduction additional del ventilation. In plus, lethargia e stupor accompaniava usualmente iste

manifestationes, sed illos esseva reversibile quandocunque le ventilation poteva esser meliorate.

Iste syndrome como accompaniamento de sever hypoventilation alveolar pote esser expectate in duo typos de patientes: (1) In patientes con restrictiones mechanic del thorace, i.e. deformitates ossee, symphyse pleural, affectiones del musculos e del nervos de respiration, etc. e (2) patientes con primari depressiones del centro respiratori inducite per drogas, anesthesia, o morbos.

In tal situationes, grande attention debe esser prestate in le administration de alte concentrationes de oxygeno e in le uso de drogas narcotic. Therapia con mesuras mechanic debe esser essayate pro alleviar le respiration e tracheotomia debe esser usate quando illo es indicate. Le melior guida practic in le recognition de un adequate ventilation es le profundor del respiration.

BIBLIOGRAPHY

1. Scholander, P. F.: Analyzer for accurate estimation of respiratory gases in one-half cubic centimeter samples, J. Biol. Chem. **167**: 235, 1947.
2. Van Slyke, D. D., and Neill, J. M.: Determination of gases in blood and other solutions by vacuum extraction and manometric measurements, J. Biol. Chem. **61**: 523, 1924.
3. Brinkman, G. L., Johns, C. J., Donoso, H., and Riley, R. L.: A modification of the method of Riley, Proemmel and Franke for determination of oxygen and carbon dioxide tensions in blood, J. Appl. Physiol. **7**: 340 (Nov.) 1954.
4. Singer, R. B., and Hastings, A. B.: An improved clinical method for the estimation of disturbances of the acid-base balance of human blood, Medicine **27**: 223, 1948.
5. Bohr, C.: Ueber die Lungenatmung, Skandinav. Arch. f. Physiol. **2**: 236, 1891.
6. Barach, A. L.: Physiological methods in the diagnosis and treatment of asthma and emphysema, Ann. Int. Med. **12**: 454, 1938–39.
7. Comroe, J. H., Jr., Bahnson, E. R., and Coates, E. O., Jr.: Mental changes occurring in chronically anoxemic patients during oxygen therapy, J. A. M. A. **143**: 1044 (July 22) 1950.
8. Sieker, H. O.: A cardiopulmonary syndrome associated with extreme obesity, J. Clin. Investigation **34**: 916, 1955.
9. Auchincloss, J. H., Jr.: Clinical and physiological aspects of a case of obesity, polycythemia and alveolar hypoventilation, J. Clin. Investigation **34**: 1537, 1955.
10. Smith, L. H.: The Medical Grand Rounds, case No. 347, Hypoventilation syndrome. Am. Pract. and Digest Treat. **7**: 1165, 1956.
11. Burwell, C. S., Robin, E. D., Whaley, R. D., and Bichelmann, A. G.: Extreme obesity associated with alveolar hypoventilation; pickwickian syndrome, Am. J. Med. **21**: 811 (Nov.) 1956.
12. Carroll, D.: A peculiar type of cardiopulmonary failure associated with obesity, Am. J. Med. **21**: 819 (Nov.) 1956.
13. Loeschke, H. H., Sweel, A., Kough, R. H., and Lambertsen, C. J.: The effect of morphine and of meperidine (Dolantin, Demerol) upon the respiratory response of normal men to low concentrations of inspired carbon dioxide, J. Pharmacol. and Exper. Therap. **108**: 376 (July) 1953.
14. Eckenhoff, J. E., Helrich, M., Hege, M. J. D., and Jones, R. E.: Respiratory hazards of opiates and other narcotic analgesics, Surg., Gynec. and Obst. **101**: 701–708 (Dec.) 1955.
15. Marshall, R., McIlroy, M. B., and Christie, R. V.: The work of breathing in mitral stenosis, Clin. Sc. **13**: 137, 1954.
16. Julich, E.: Ueber die Ursachen der cardialem und pulmonalen Dyspnoe, Ztschr. f. d. ges. exper. Med. **121**: 535, 1953.
17. Briscoe, W. A., Forster, R. E., and Comroe, J. H., Jr.: Alveolar ventilation at very low tidal volumes, J. Appl. Physiol. **7**: 27, 1954.

A COMPARISON OF THE PLASMA IRON, IRON-BINDING CAPACITY, STERNAL MARROW IRON AND OTHER METHODS IN THE CLINICAL EVALUATION OF IRON STORES *

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Correct evaluation of the iron stores helps the clinician to distinguish the anemia of iron deficiency from that of chronic infection, renal disease and cancer. It makes possible a presumptive diagnosis of hemochromatosis. We have recently reviewed methods of evaluating the iron stores.[1] Several of these appear to have considerable merit, and it is unfortunate that they have been neglected by most physicians.

The most direct method of assessing the iron stores is the examination of fragments of sternal bone marrow for stainable iron. Although on occasion this method may give misleading results, it has been found to be highly satisfactory in the hands of almost all the investigators who have used it.[2-9] It has also been suggested that the percentage of stainable iron-containing normoblasts (sideroblasts) in smears of sternal bone marrow be used as a means of detecting iron deficiency.[10] Both of these methods require that the patient be subjected to the discomfort and risk of a marrow puncture. A less direct but nevertheless accurate substitute would therefore be most desirable. Determination of the plasma iron concentration and the unsaturated iron-binding capacity has been employed for this purpose. Most patients with iron deficiency anemia have been found to have a low plasma iron and elevated iron-binding capacity. In the anemia of chronic disease the plasma iron concentration tends to be low, but the unsaturated iron-binding capacity also tends to be diminished. In cases of hemochromatosis, the plasma iron is usually high and the unsaturated iron-binding capacity is decreased greatly.[11, 12, 13] The degree of saturation of the iron-binding protein with iron is a useful single parameter that takes into account both the plasma iron and the iron-binding capacity.[12, 13]

There are also several other possible substitutes for bone marrow examination in the evaluation of the iron stores. These include the oral iron tolerance test and studies of ferrokinetics with radioactive iron. Several groups of European workers have used the oral iron tolerance test as sole

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evidence of depletion of iron stores.[14, 15, 16] Although, to our knowledge, radioiron has never been systematically used for the estimation of the iron stores, but rather as a means for studying erythropoiesis, it is well known that the plasma clearance of iron tends to be more rapid in iron-deficient than in normal subjects, and that the plasma clearance tends to be abnormally slow in subjects with hemochromatosis.[17] Incorporation of iron into red cells appears to be more nearly complete in iron-deficient subjects than in normal subjects or those with an excess of iron load.[17]

An adequate comparison of these methods has not been made previously. This study was carried out to determine to what extent these means of assessing iron stores may be substituted for one another, and what may be expected from each in a variety of clinical situations. Special emphasis has been placed on the diagnosis of the mildest degree of iron depletion. This is a particularly important problem because of the frequency with which it occurs and because the hypochromia and microcytosis which are so characteristic of severe iron deficiency anemia often are not present in the early stages of its development.[18, 19]

Materials and Methods

A. *Patients:* Included in this study are all patients upon whom both plasma iron determinations and bone marrow examinations have been carried out at The University of Chicago Clinics from July, 1955, through December, 1956. When pertinent, earlier studies on the same patients are also presented. A few patients in whom the follow-up was insufficient to permit a diagnosis to be made have been excluded. Otherwise, there has been no selection of cases; a total of 106 subjects was studied. The patients have been classified into six groups according to the diagnosis: (1) Iron deficiency anemia. In all of these individuals the diagnosis was confirmed by adequate response to iron therapy. (2) Thalassemia minor. In each case the diagnosis was confirmed by appropriate laboratory means, including in most cases alkali denaturation studies of the hemoglobin and the determination of red cell fragility. (3) Other anemias. (4) Miscellaneous disorders (without anemia). (5) Idiopathic hemochromatosis. In each of these patients the diagnosis was confirmed by liver biopsy unless otherwise indicated. (6) Excessive fatigue not associated with anemia. No abnormality could be discovered in any of the patients in this group by the use of appropriate laboratory and clinical methods. Examinations of their iron stores were carried out as the first stage of a study designed to determine whether preanemic iron depletion is symptomatic.

B. *Marrow Samples:* All marrow specimens were obtained by aspiration from the sternum with an 8-gauge needle, except for one specimen, which was obtained by surgical biopsy. Fragments of marrow were fixed in Zenker's formol. After being dehydrated and imbedded in nitrocellulose,

the marrow fragments were sectioned at 6 μ. They were stained for iron for 30 minutes, using a freshly mixed solution made from equal parts of 4% potassium ferrocyanide and 4% hydrochloric acid which had been heated to 56° C. The sections were counterstained with hematoxylin and eosin. Iron stains a brilliant blue color with this technic. In spite of great care, blue-staining artifacts occurred with some frequency. With experience, these may usually be readily distinguished from true intracellular storage iron by their obviously extracellular position and their frequently irregular and sharply angular character as compared with the more rounded intracellular granules or masses of true storage iron. Occasionally, most of the cytoplasm of reticulum cells took a rather diffuse blue stain. This, too, was regarded as being true storage iron, but diffusely-staining blue areas not

TABLE 1

Group 1, Iron Deficiency Anemia

Case No.	Additional Clinical Data	Sex	Hb gm. %	PI* γ%	IBC† γ%	Bone Marrow Iron	Additional Iron Studies
1	Menorrhagia	F	2.4	7	430	0	
2	Amebiasis	F	5.6	30		0	
3	Bleeding hemorrhoids	M	6.2	<5	500	0	
4	Ulcerative colitis—60 transfusions in last year	F	6.9	<5	430	Trace	2% sideroblasts
5	G-I bleeding	F	7.3	<5	300	0	0% sideroblasts
6	Menorrhagia	F	7.7	15	374	0	
7	Menorrhagia	F	7.9	7	470	0	0% sideroblasts
8	Menorrhagia, steatorrhea	F	8.6	<5	350	0	
9		F	8.6	6	428	0	
10	7 mos. pregnant	F	8.8	50	320	0	
11	Menorrhagia—blood transfusion 1 mo. prior to examination	F	8.8	10	300	0	
12		F	9.7	37	250	++	
	1 year later, interim iron treatment		12.4	155	160	+	20% sideroblasts
13		F	9.9	7	375	0	0% sideroblasts
14	Ulcerative colitis—blood transfusion given 2 weeks prior to examination	F	11.0	7	215	0	0% sideroblasts
15		F	11.0	34		0	
16	History of multiple transfusions	F	11.0	46	430	0	Oral iron tolerance test

TABLE 1—(*Continued*)

Case No.	Additional Clinical Data	Sex	Hb gm. %	PI* γ%	IBC† γ%	Bone Marrow Iron	Additional Iron Studies
17	G-I bleeding of unknown origin	F	11.1	70	265	0	
18	Menorrhagia	F	11.2	90	0	0	
19	Menorrhagia	F	11.3	25	480	0	0% sideroblasts
20	Rheumatic fever	F	11.3	10	285	0	
21	Menorrhagia	F	11.3	90	—	0	
22		F	11.4	50	150	0	
	1 year later, no iron treatment had been given		7.3	15	475	0	
23	Menorrhagia	F	11.5	25	375	0	0% sideroblasts
24	5 mos. post-transfusion	F	11.6			++	
	4 years later, no iron treatment had been given		11.5	78 44 65	160	0	Radioiron studies, oral iron tolerance test
	7 mos. after 950 mg. saccharate iron oxide given I.V.		12.2	160	100	++‡	
25	G-I bleeding	M	11.7	25	—	0	
26	History of thrombocytopenic purpura, treated by splenectomy	F	11.7	125	155	0	
27	Diaphragmatic hernia	M	12.3	25	—	0	
28	Duodenal ulcer	M	12.3	34	375	0	
29	See table 6, group 6						

* PI = plasma iron.
† IBC = unsaturated iron-binding capacity.
‡ Iron distributed in many small, equal-sized granules.

related to the cellular structure represent artifacts. The marrow sections were identified only by number when examined. A quantitative appraisal of the amount of iron seen in the iron-stained sections was made. If no iron was seen in 50 or more oil immersion fields of marrow, the amount of iron was classified as "0." If, on the examination of 50 or more oil immersion fields, only very rare intracellular iron granules or blue-staining reticulum cells were seen, the iron content of the marrow was classified as "trace." If intracellular iron granules or blue-staining reticulum cells were seen occasionally, but the amount of iron appeared to be distinctly less than normal, the iron content of the marrow was graded "+." A normal amount of iron in the marrow sections was classified as "2+" (iron granules present in 10% or more, but not in every oil immersion field examined).

TABLE 2

Group 2, Thalassemia Minor

Case No.	Additional Clinical Data	Sex	Hb gm. %	PI* γ%	IBC† γ%	Bone Marrow Iron	Additional Iron Studies
30	7th month of pregnancy	F	9.8	50	265	++	60% sideroblasts
31		F	10.0	127	210	+++	Oral iron tolerance test
32		F	10.2	138	—	++	
33		F	10.4	180 138	105 70	++	
34		F	11.0	65	235	++	25% sideroblasts
35	18 transfusions over a period of several years	F	11.5	34 50	300 250	+++	
36	Prolonged iron treatment including I.V. saccharated iron oxide; secondary hemochromatosis	F	11.5	170 185 155	0 50 50	+++	Radioiron studies
37		F	11.7	90	215	++	
38	Daughter of case 36	F	11.8	34	215	++	
39	Hyperthyroidism	F	12.1	70	115	++	

* PI = plasma iron.
† IBC = unsaturated iron-binding capacity.

A moderate increase (considerable amounts of iron in virtually every oil immersion field) was designated as "3 +." The designation "4 +" was reserved for the most spectacular degree of iron excess in the marrow.

In some instances, counts of sideroblasts were made on smears of the marrow aspirate prepared according to the method of Kaplan et al.[10] The freshly made smears were fixed in formalin vapor for at least one-half hour and were then stained for one hour in a freshly mixed solution containing equal parts of 2% hydrochloric acid and 2% potassium ferrocyanide. A counterstain of carbolfuchsin was applied. Twenty to 50 normoblasts were examined for the presence of granules of stainable iron.

C. *Plasma Iron and Serum/Unsaturated Iron-binding Capacity Determinations:* Plasma iron determinations were carried out according to the method of Barkan and Walker.[20] Although some extraordinarily low plasma iron values were obtained, complete recovery of small amounts of added iron was achieved using this method, and we regard the results as quite reliable. The unsaturated serum iron-binding capacities were determined on fresh sera by the method of Rath and Finch.[12] Results obtained on sera showing evidence of hemolysis have been excluded. Fasting morning specimens were usually used, but in a few instances determinations were carried out on postprandial specimens.

D. *The Oral Iron Tolerance Test:* Oral iron tolerance tests were carried out according to the method of Jasinski.[14] Ferrous gluconate containing approximately 165 mg. elemental iron was administered to the fasting patient at 8:00 a.m. Plasma iron determinations were carried out before the orally administered dose of iron, and at one, three and usually seven hours afterwards. The patient was not allowed to eat until three hours after administration of the iron.

E. *Radioiron Studies:* Radioiron, as ferrous-59 citrate, was incubated with plasma for 15 to 30 minutes at 37° C., and the labeled plasma was injected intravenously; in some cases the Fe^{59} citrate was diluted in saline and

TABLE 3

Group 3, Miscellaneous, Anemic

Case No.	Additional Clinical Data	Sex	Hb gm. %	PI* γ%	IBC† γ%	Bone Marrow Iron	Additional Iron Studies
40	Hyperthyroidism, epistaxis; Hb returned to normal on treatment with iron and I^{131}	F	9.4	90	250	+	
41	Hyperthyroidism	F	10.4	10	265	+++	
42	Myxedema	F	11.8	105	105	+++	
43	Carcinoma of lung	M	9.8	70	225	++	
44	Acute myelogenous leukemia, preëxisting polycythemia rubra vera	M	9.4	127	50	+++	95% sideroblasts
45	Subacute myelogenous leukemia; several blood transfusions	F	4.2	170	0	+++	40% sideroblasts
46	Subacute myelogenous leukemia	F	7.4	50	235	+++	
47	Reticulum cell sarcoma	F	6.0	170	50	+++	
48	Hodgkin's disease	M	10.7	37	214	+	
49	Hodgkin's disease	F	8.0	138	0	++++	
50	Myelofibrosis	M	6.9	20	240	+	Radioiron studies
51	Chronic myelogenous leukemia; bleeding hemorrhoids	M	11.3	50	175	0	
52	Subacute myelogenous leukemia; multiple transfusions	F	5.2	235	0	++++	
53	Chronic nephritis, epistaxis, menorrhagia	F	4.6	50	100	++++	57% sideroblasts
54	Uremia, malnutrition, many blood transfusions	F	8.1	34	250	++++	30% sideroblasts

TABLE 3—(*Continued*)

Case No.	Additional Clinical Data	Sex	Hb gm. %	PI* γ%	IBC† γ%	Bone Marrow Iron	Additional Iron Studies
55	Diabetic nephrosclerosis, occasional melena	F	6.1	70	107	++	Radioiron studies
56	Disseminated lupus erythematosus, menorrhagia	F	10.8	34	225	0	
57	Disseminated lupus erythematosus, history of transfusions	F	11.1	95	150	+++‡	
58	Anemia of undetermined etiology	M	12.5			+++	
	2 yrs. later, pernicious anemia		9.5	127	150	++++	
59	Pernicious anemia	M	9.9			+++	
	6 mos. later, pernicious anemia adequately treated, bleeding carcinoma of cecum		11.8	168	240	Trace	
60	Postgastrectomy, pernicious anemia, history of bleeding ulcer	M	11.3	34	—	0	
61	Pernicious anemia	M	12.3	150	158	++++	
62	Sprue syndrome	M	10.6	150	35	+++	
63	Subacute bacterial endocarditis	M	7.1	15 7	110 100	++++	Oral iron tolerance test 4% sideroblasts
64	Anemia following irradiation for duodenal ulcer	M	11.3	90	200	Trace	
65	Postgastrectomy for hemorrhagic gastritis; 12,000 c.c. blood given 1 mo. previously	M	11.2	10	235	++++	
66	Bleeding duodenal ulcer	M	13.0	95	200	++	

* PI = plasma iron.
† IBC = unsaturated iron-binding capacity.
‡ Iron distributed in many small, equal-sized granules.

injected intravenously. Blood samples were obtained at suitable intervals, and the plasma radioactivity was measured in a well-type scintillation counter. The percentage of radioiron incorporated into the red cell mass was determined by measuring the radioactivity of blood samples at suitable intervals, in most instances until a constant level of radioactivity had been reached. The red cell mass was measured with sodium chromate-51-labeled red blood cells, according to the technic we have previously described,[21] or calculated from the plasma volume by extrapolation of the radioiron clearance curve to the time of injection. A venous hematocrit/total-body hematocrit ratio of 0.93 was used. The turnover of plasma iron, expressed

as mg./100 c.c. whole blood/day, was calculated according to the method of Bothwell et al.[22]

F. *Hemoglobin Determinations:* The hemoglobin concentration in the peripheral blood was determined spectrophotometrically as oxyhemoglobin.

Results

A. *The Iron Content of Bone Marrow Sections* (Tables 1–7): GROUP 1 (iron deficiency anemia). The appraisal of the amount of iron in the bone marrow sections is presented, together with pertinent clinical data, in table 1. There was generally excellent agreement between the clinical diagnosis and the amount of iron seen in the bone marrow sections. Stainable iron was present in only four of the 31 marrow samples from 29 patients with iron-sensitive anemia. All but one of the patients from whom these four samples were obtained had recently received either blood transfusions

TABLE 4

Group 4, Miscellaneous, Nonanemic

Case No.	Additional Clinical Data	Sex	Hb gm. %	PI* γ%	IBC† γ%	Bone Marrow Iron	Additional Iron Studies
67	Hypertension	M	16.5	100	200	++	
68	History of auto-immune hemolytic anemia with 43 blood transfusions several years previously	F	13.1	50	115	++++	
69	History of anemia, etiology undetermined	F	12.8	100	160	+++	
70	Fever of undetermined origin	F	13.1	65	210	+++	
71	Myxedema	F	15.0	75	160	+	
72	Brother of patient with idiopathic hemochromatosis	M	15.2	175 190	125 145	++	
73	Anxiety state, menorrhagia	F	14.4	90	168	+	
74	Leukopenia of unknown etiology	F	12.3	85	—	++	
75	Secondary hemochromatosis treated by multiple phlebotomy	M	15.0	10	—	0	
76	Congestive heart failure, hypersplenism	F	13.1	70	225	+	
77	Cirrhosis, diabetes; no iron excess in liver; history of receiving 300 mg. iron intravenously as iron cacodylate	M	14.2	200 200	0 0	+++	Radioiron studies
78	Scleroderma	F	12.0	50	105	++	

* PI = plasma iron.
† IBC = unsaturated iron-binding capacity.

TABLE 5

Group 5, Idiopathic Hemochromatosis

Case No.	Additional Clinical Data	Sex	Hb gm. %	PI* γ%	IBC† γ%	Bone Marrow Iron	Additional Iron Studies
79	7,000 c.c. blood removed. No phlebotomies for past 2½ weeks	F	14.2	240	0	+++‡	49% sideroblasts
80	Untreated	M	12.3	240	0	+++‡	
81	Diagnosis not definitely established. Liver biopsy inadequate	F	11.0	150	150	++++	
82	Untreated	M	15.0	150	56	+++‡	
83	Untreated	M	14.6	190	100	+++‡	
	3 mos. after initial examination; 10,000 c.c. blood have been removed		10.5	217			
	4½ mos. after initial examination; 15,000 c.c. blood have been removed		10.7	257	72		
	14 mos. after initial examination; 35,000 c.c. blood have been removed		11.9	25 46	200 265	++‡	10% sideroblasts

* PI = plasma iron.
† IBC = unsaturated iron-binding capacity.
‡ Iron distributed in many small, equal-sized granules.

or intravenously administered saccharated iron oxide. Although this patient (case 12) conforms to our criteria for the diagnosis of iron deficiency, it is conceivable that her anemia was due to another cause, and that the response during iron administration was coincidental.

GROUPS 2 and 3 (thalassemia and other anemias) (tables 2 and 3). More than a trace of iron was found in all but cases 51, 56, 59 and 60. In all of these patients there was a history of excessive blood loss. Frank iron excess was present in about one-half of the patients in groups 2 and 3, presumably because of the shift of iron from the red cell mass to stores that occurs in anemia, and because of blood transfusions and iron therapy.

GROUP 4 (miscellaneous disorders without anemia) (table 4). Iron was present in all but one patient (case 75). He had been subjected to multiple phlebotomies. Excessive iron deposits were observed only occasionally, chiefly in patients with a history of anemia.

GROUP 5 (hemochromatosis) (table 5). In untreated hemochromatosis, some iron excess was observed in each case, although the amount present was not spectacular. After treatment by phlebotomy, less iron was found in the marrow. A striking characteristic of the marrow iron in each case of proved primary hemochromatosis we have examined is the occurrence of many equal-sized granules of iron, packed closely together in a relatively

few reticulum cells. A similar appearance of bone marrow iron was noted in patients who had been treated by intravenous administration of saccharated iron oxide.

GROUP 6 (fatigue, without anemia) (table 6). Stainable iron was absent from six and markedly reduced in six of the 24 bone marrow specimens obtained from 24 nonanemic women who suffered from excessive fatigue.

B. *Sideroblast Counts:* GROUP 1. Only 0 to 2% of the erythroblasts in marrow smears from five patients with iron deficiency anemia contained granules of stainable iron.

GROUPS 2 and 3. In contrast, 4 to 95% of the normoblasts of patients with other types of anemia contained stainable iron granules. Within this group of patients, the number of sideroblasts was of no value in estimating the size of the iron stores: the patient with the lowest sideroblast count had one of the largest amounts of iron in the marrow.

TABLE 6

Group 6, Nonanemic, Fatigue

Case No.	Additional Clinical Data	Sex	Hb gm. %	PI* γ%	IBC† γ%	Bone Marrow Iron	Additional Iron Studies
29		F	14.2	60 55 65	224 280	0	Radioiron studies
	4 mos. after 950 mg. saccharated iron oxide had been given; anemia responded to further iron therapy		10.0	5	360	++‡	
84		F	12.3	10	315	0	Radioiron studies
85		F	12.1	81	140	0	
86		F	13.5	127 109 50	112 127 —	0	Radioiron studies; oral iron tolerance test
87		F	12.0	44	320	0	0% sideroblasts
88		F	13.8	37 25	430 320	0	0% sideroblasts
89		F	14.9	75	265	Trace	
90		F	13.1	90 105	107 215	Trace	Oral iron tolerance test
91	History of iron deficiency treated with oral iron	F	13.8	105	—	Trace	Oral iron tolerance test; radioiron studies
	6 mos. later—continued oral therapy		12.3	65	100	Trace	

TABLE 6—(*Continued*)

Case No.	Additional Clinical Data	Sex	Hb gm. %	PI* γ%	IBC† γ%	Bone Marrow Iron	Additional Iron Studies
92		F	13.9	117	190	Trace	
93		F	13.4	165	—	Trace	
94		F	13.5	122	160	+	40% sideroblasts
95		F	13.5	70	200	+	35% sideroblasts
96		F	12.6	125	115	++	
97		F	12.7	107	160	++	
98		F	12.3	85	215	++	20% sideroblasts
99		F	13.6	127	112	++	
100		F	14.3	112	254	++	
101		F	12.3	90		++	
102		F	13.8	127	168	++	
103		F	14.8	107	168	++	
104		F	13.3	80	215	+++	41% sideroblasts
105		F	13.1	90	160	+++	
106		F	13.1	105	107	+++	

* PI = plasma iron.
† IBC = unsaturated iron-binding capacity.
‡ Iron distributed in many small, equal-sized granules.

TABLE 7

The Relationship of Clinical Diagnosis to Bone Marrow Stainable Iron

Clinical Diagnosis	Bone Marrow Stainable Iron					
	0	Trace	+	++	+++	++++
Untreated iron deficiency anemia	25	0	0	1	0	0
Parenterally treated iron deficiency anemia in relapse	2	1	0	2	0	0
Thalassemia minor	0	0	0	7	3	0
Miscellaneous anemias	3	2	3	3	10	8
Miscellaneous nonanemic	1	0	3	4	3	1
Untreated idiopathic hemochromatosis	0	0	0	0	3	1
Nonanemic fatigue	6	6	2	8	3	0

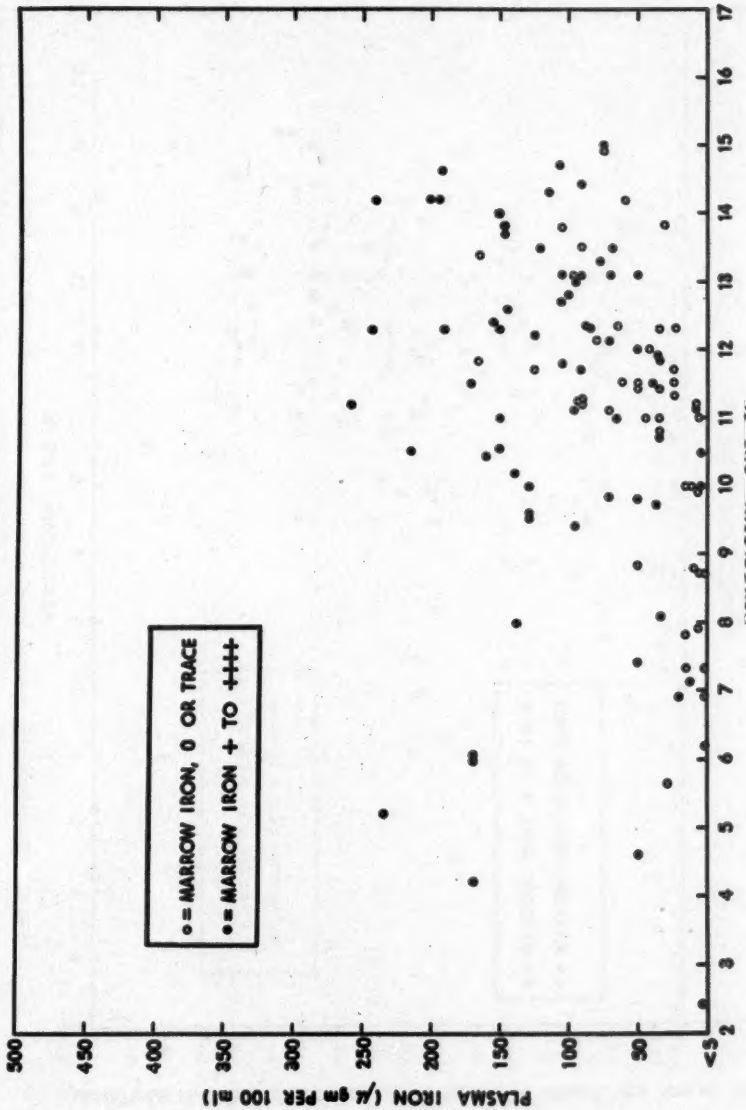

FIG. 1. The relationship between bone marrow iron, plasma iron and hemoglobin level.

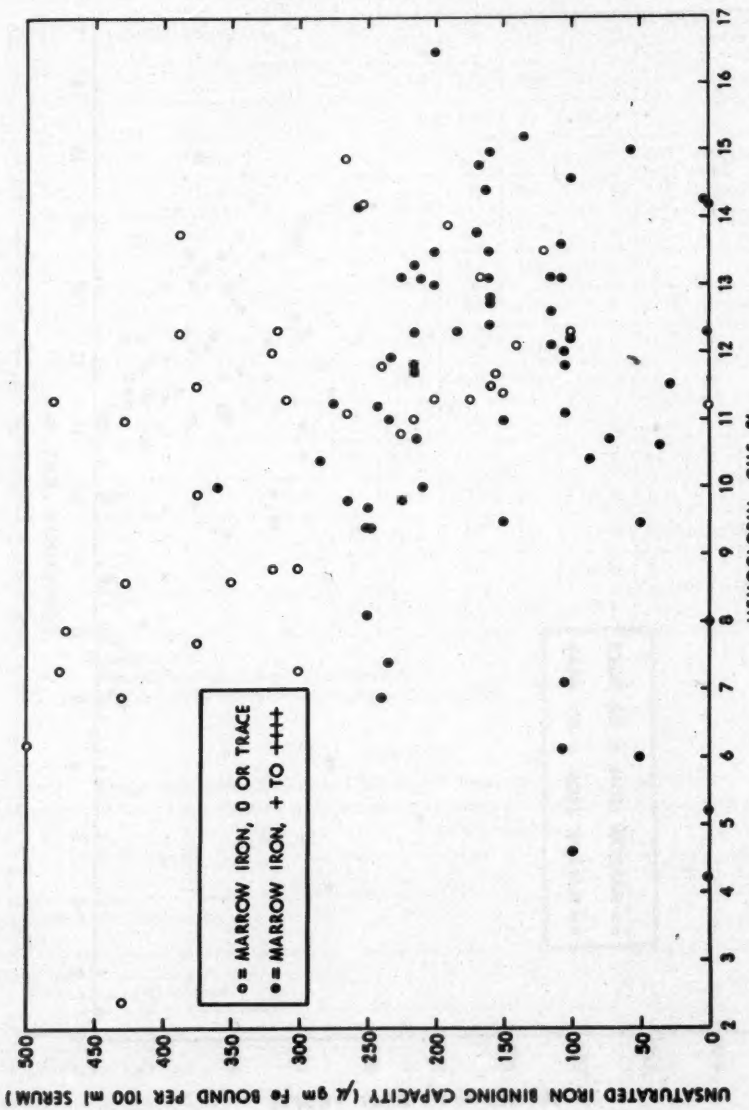

FIG. 2. The relationship between bone marrow iron, serum unsaturated iron-binding capacity and hemoglobin level.

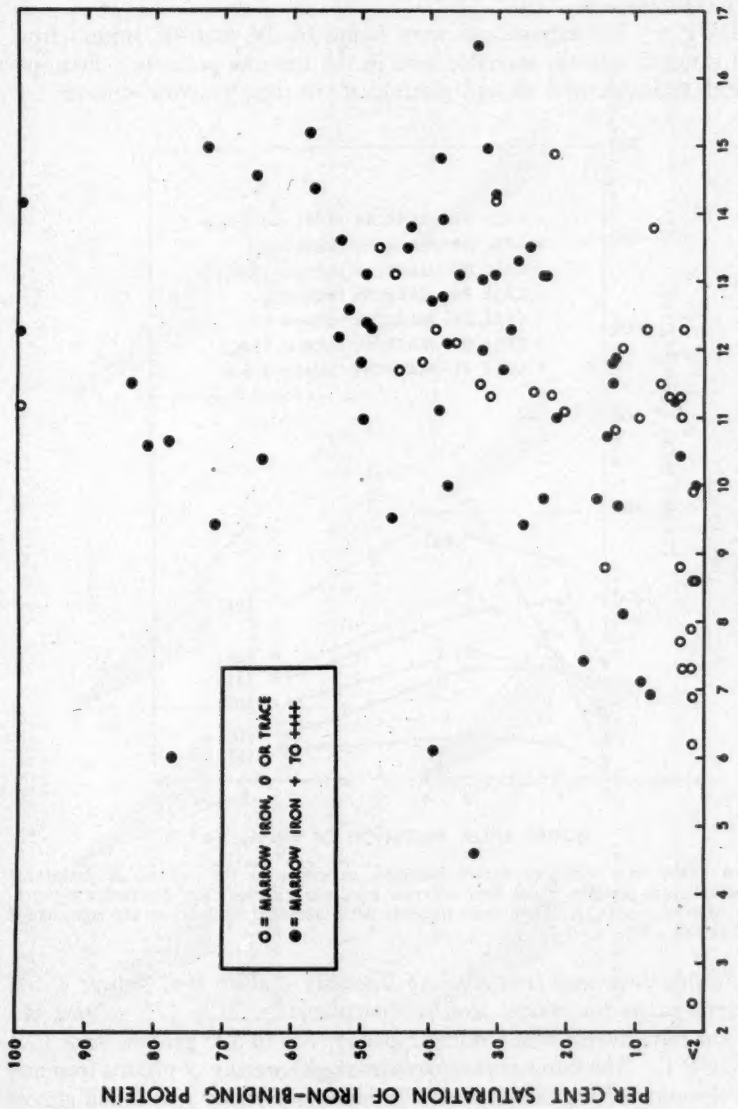

FIG. 3. The relationship between bone marrow iron, the degree of saturation of iron-binding protein and hemoglobin level.

GROUP 5. The sideroblast counts were not unusually high in patients with hemochromatosis.

GROUP 6. No sideroblasts were found in the marrow smears from the two patients with no stainable iron in the marrow sections. Four patients with stainable iron all had sideroblasts in their marrow smears.

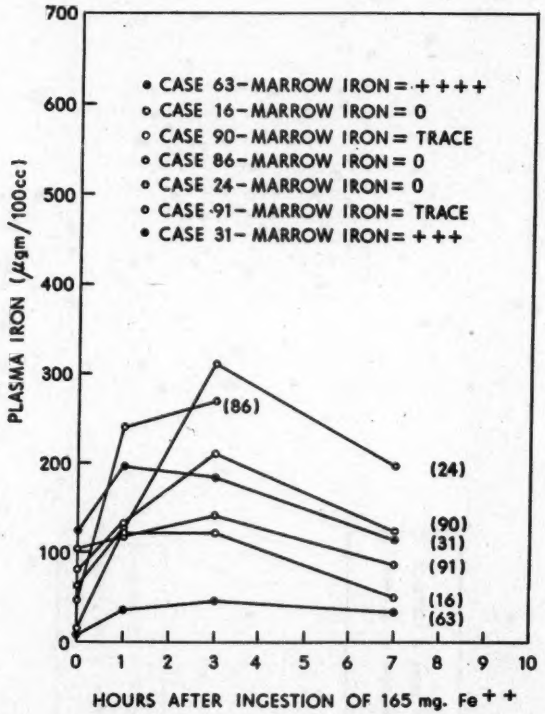

FIG. 4. Oral iron tolerance curves obtained according to the method of Jasinski.[14] Data obtained from patients whose bone marrow iron was histologically depleted are represented by open circles (○). Data from patients with increased iron stores are represented by closed circles (●).

C. *Plasma Iron and Iron-Binding Capacity (tables 1–6, figures 1–3):* The normal range for plasma iron is approximately 70 to 175 gamma %; that for the unsaturated iron-binding capacity, 100 to 300 gamma %.[1]

GROUP 1. The familiar picture of marked lowering of plasma iron and marked elevation of the unsaturated iron-binding capacity was found almost invariably in the severer grades of iron deficiency, but much less commonly in the patients with mild iron deficiency anemia. Thus it is apparent from figure 3 that the percentage of saturation of iron-binding protein with iron was uniformly low in subjects with hemoglobin values of less than 8.8 gm.

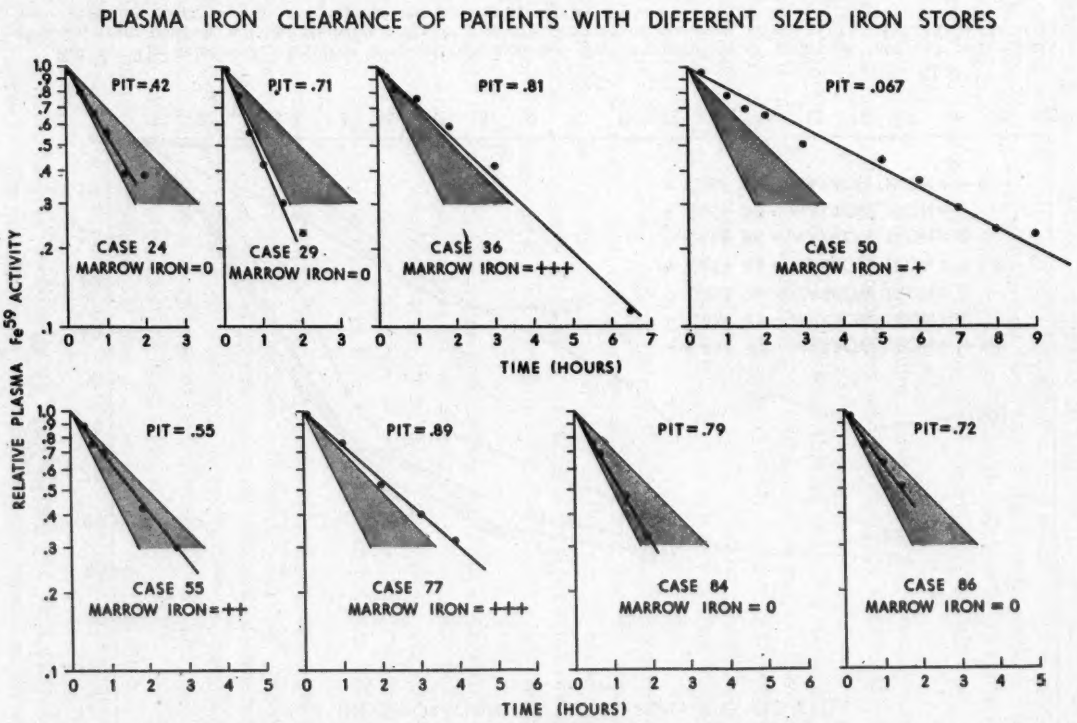

FIG. 5. Clearance of radio iron from plasma of eight patients. In each case the plasma iron turnover (PIT) is presented as milligrams of iron turned over per 100 c.c. of whole blood per 24 hours.[22] The shaded area represents normal range for clearance of iron from the plasma. In each case the histologic evaluation of marrow iron is also given.

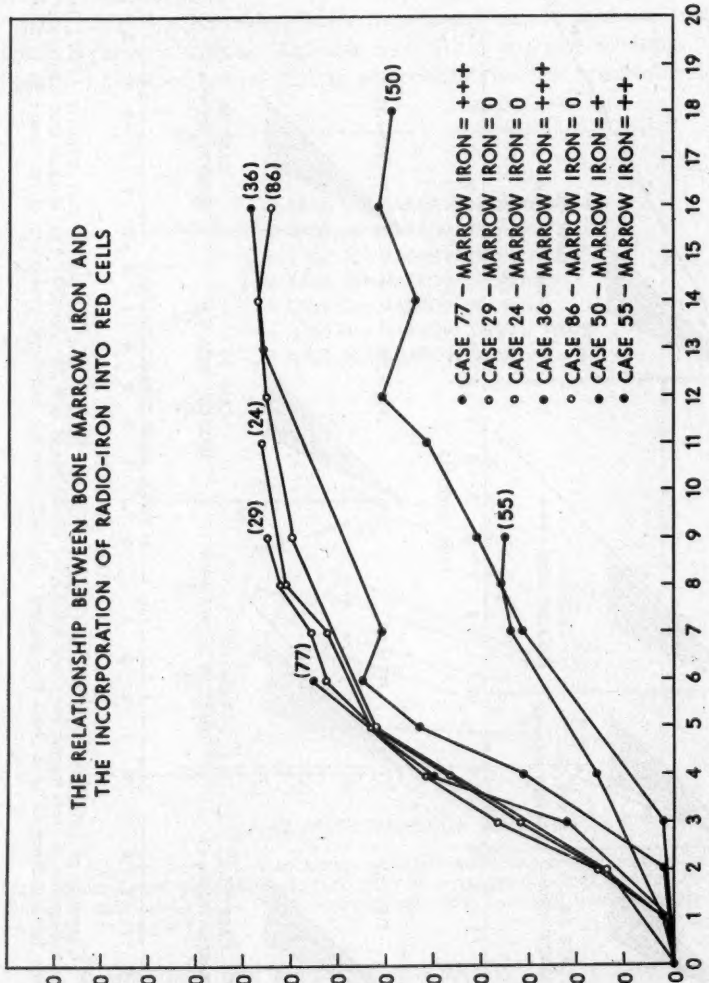

FIG. 6. The relationship between bone marrow iron and the incorporation of radioiron into red cells. Data obtained from patients without stainable marrow iron are represented by open circles (○). Data from patients with stainable marrow iron are represented by closed circles (●).

%. With less severe grades of anemia, on the other hand, the percentage saturation was often much higher. A synthesis of the data from many patients with varying degrees of iron deficiency would make it appear that the onset of the anemia antedates the onset of the hypoferremia. This conclusion is borne out in the single case in which, because of an error in diagnosis, we have been able to observe development of iron deficiency anemia (case 22).

GROUP 2. In thalassemia minor, borderline or low plasma iron values with normal iron-binding capacities were encountered in several instances (cases 30, 34, 35 and 38).

GROUP 3. In anemias other than that of iron deficiency and thalassemia minor, the plasma iron is also frequently lowered. However, pronounced elevations of the iron-binding capacity (above 300%) were not observed. The percentage saturation of the iron-binding protein was therefore often reduced but was greater than that of severely anemic iron-deficient subjects.

GROUP 5. In each case of untreated hemochromatosis proved by liver biopsy, the plasma iron was elevated and the iron-binding capacity was diminished. In the one case studied after 35,000 c.c. of blood had been removed by phlebotomy, the fall in the plasma iron preceded depletion of the stainable iron stores. This confirms the observations reported recently by Finch and Finch.[23]

GROUP 6. The plasma iron and plasma iron-binding capacities in nonanemic women failed, in general, to distinguish those with histologically demonstrable iron depletion from those whose iron stores were normal or even increased. Occasionally, however, low plasma iron values and high saturated iron-binding capacities were encountered in patients with depleted iron stores.

D. *Oral Iron Tolerance Tests:* The results of oral iron tolerance tests on seven patients are presented in figure 4. Jasinski,[14] the chief proponent of this method of evaluating iron stores, has never established clearcut standards for interpretation of these curves in the evaluation of iron stores, but he does indicate that a large rise proves iron depletion. Even from the limited number of cases reported here, however, it is evident that there is little relationship between the size of iron stores, determined by marrow biopsy, and either the percentage rise or absolute height of the oral iron tolerance curve.

E. *Radioiron Studies:* Studies with radioiron have been carried out on nine patients. The clearance of radioiron from the plasma is presented in figure 5. Although the clearance rate of the iron-depleted patient is more rapid than that of the patient with normal or increased iron stores, both are very close to the normal range (one-half clearance time of from one to two hours). The percentage of radioiron incorporated into the red cell mass was measured in seven patients and is shown in figure 6. The iron-depleted

patients appear to incorporate radioiron into their red cell mass more rapidly for the first few days after it is given, but the difference between the iron-depleted patients and those with adequate or increased iron stores is small, and ultimately the percentage of iron incorporated seems to be almost entirely independent of the size of the iron stores.

Discussion and Conclusions

The results of this study show that the most reliable means of diagnosing iron deficiency was the examination of sternal bone marrow sections for stainable iron. Counts of the number of sideroblasts in bone marrow also seem reliable in our limited experience, but in the hands of others the method has not been entirely satisfactory. Douglas and Dacie [24] found that absence of stainable iron from marrow sections did not necessarily mean that sideroblasts would be absent. Conversely, Morse and Read [25] found no sideroblasts in the bone marrow of some patients with marked hypoferremia of chronic inflammation who had adequate iron stores. Although the enumeration of sideroblasts certainly seems to have some real merit, except for its technical simplicity it offers no advantage over the direct evaluation of bone marrow iron stores.

The plasma iron determination alone was of little value. The plasma iron, combined with the determination of the iron-binding capacity, was a reliable means of detecting iron deficiency when the anemia was severe (below 9 gm.%). When the hemoglobin was higher than 9 gm.%, however, the plasma iron and iron-binding capacity became a much less reliable index of iron depletion. A normal plasma iron and iron-binding capacity cannot be regarded as excluding the diagnosis of iron deficiency in patients with mild anemia. Unfortunately, it is in these patients that the characteristic hypochromia and microcytosis of iron-deficiency anemia may often be absent,[18, 19] and that the diagnosis is most often obscure. Occasionally, in actively bleeding patients, a low plasma iron and high iron-binding capacity have been observed even when adequate iron stores were present in the marrow. In the present study this was particularly true in patients who had been treated with intravenous saccharated iron oxide or blood transfusions. Persistence of some parenterally-administered iron, even after relapse of iron deficiency anemia, has been reported previously by Davidson and Jennison,[8] and is referred to by Stevens, Coleman and Finch.[5] We have also observed this dissociation between the plasma iron and iron-binding capacity and the bone marrow iron in an actively bleeding patient who had not received such therapy.[18] Presumably a portion of the iron stores is not mobilized with sufficient rapidity to meet the needs of the body for iron when the need is acute.

Our inability to differentiate cases of thalassemia minor from those of mild iron deficiency by means of the plasma iron and iron-binding capacity

is particularly important, since what little evidence has been published on the plasma iron in thalassemia minor suggests that it tends to be elevated.[26] This was by no means true in all of our cases. In some patients (cases 30, 34, 35 and 38), it was actually abnormally low. Differentiation of iron deficiency from thalassemia is often difficult, and the examination of the sternal marrow for stainable iron appears to be the best solution of this diagnostic problem. This is in agreement with the data of Wallerstein and Aggeler.[27]

We have been unable to find any acceptable evidence that the iron tolerance curve is a valid means of assessing the iron stores, even though it has been used extensively for this purpose.[1] From our limited experience, this technic seems worthless for evaluating iron stores. The shape of the iron tolerance curve undoubtedly depends on several factors that are completely independent of storage iron.

Although radioiron plasma clearance and red cell uptake are influenced by the size of the iron stores, many other factors are also operative. The differences between the radioiron curves of iron-depleted patients and those with excess iron are so slight that these methods seem to be of little help in evaluating the size of the iron stores.

It has not yet been established clearly whether iron depletion without anemia is symptomatic, as has been suggested by some European workers on the basis of very questionable evidence,[15, 28, 29] or whether it is "subclinical," as has been suggested by Stevens et al.[5] This important problem has received practically no attention in this country. The present study indicates that the diagnosis of "iron deficiency without anemia" can be made only on the basis of study of the sternal marrow iron. In the diagnosis of iron depletion without anemia, the plasma iron and serum iron-binding capacity, the results of iron tolerance curves and radioactive studies are of little or no help. The treatment of several of the iron-depleted patients in Group 6 with iron has resulted in a rather impressive ameliorization of their symptoms.[18] A placebo effect has not been excluded, however, and a double-blind study is under way to determine the clinical significance of this condition.

Summary

1. Histologic examination of bone marrow sections, enumeration of sideroblasts in marrow smears, the plasma iron and iron-binding capacity, oral iron tolerance tests, and radioiron studies have been compared as means of evaluating the iron stores.

2. Examination of the bone marrow for stainable iron was the most reliable means of differentiating iron deficiency from the other forms of anemia. It was the only means by which sideropenia without anemia could be diagnosed. The amount of iron in the marrow in hemochromatosis was not greatly excessive, but the pattern of deposition was distinctive.

3. The enumeration of sideroblasts appeared to be a reliable means of detecting iron deficiency, but seemed to offer little advantage over evaluation of iron stores in sections of marrow.

4. The plasma iron and iron-binding capacity studies were reliable means of diagnosing iron deficiency only when the hemoglobin was below 9 gm.%. In less severely anemic patients it was of little help in differentiating iron deficiency from other types of anemia. The plasma iron was increased markedly and the unsaturated iron-binding capacity was decreased in all patients with primary hemochromatosis.

5. The iron tolerance curve correlated so poorly with the iron stores as to be an entirely worthless means of evaluating the iron stores.

6. The plasma clearance and red cell utilization of radioiron were not affected sufficiently by the size of iron stores to make this a practical means of measuring iron stores.

Summario in Interlingua

Le correcte evalutation del reservas de ferro adjuta le clinico a distinguer le anemia de carentia de ferro ab altere anemias. Le methodos que ha essite proponite pro le evalutation quantitative del reservas de ferro include le examine de particulas de medulla sternal pro le presentia de ferro colorabile, le numeration del normoblastos a contento de ferro colorabile in frottis de medulla, le mesuration de ferro de plasma e del non-saturate capacitate ferro-ligante in le sero, le test del tolerantia oral, e studios ferrocinetic con ferro radioactive. Le presente studio include omne le patientes pro qui, in le curso de un periodo de un anno e medie, non solmente evalutationes del ferro de medulla ossee e del ferro de sero sed etiam determinationes del capacitate ferro-ligante habeva essite executate. Iste patientes esseva gruppate in sex categorias: (1) Casos de anemia a carentia de ferro, confirmate per adequate responsas a therapia con ferro, (2) casos de thalassemia minor, (3) casos de altere anemias, (4) casos de miscellanee disordines sin anemia, (5) casos de hemochromatosis idiopathic, e (6) casos de fatiga excessive non associate con anemia o altere demonstrabile disordines organic. Le resultatos del studio confirma le these que le observation de ferro colorabile in medulla ossee representa un excellente methodo pro deteger anemia a carentia de ferro. Solmente un del 26 patientes in Gruppo 1 habeva in su medulla ferro de forma colorabile. Le numeration de sideroblastos se revelava como un methodo fidel pro le detection de carentia de ferro, sed il pareva que illo offereva pauc avantages in comparation con le evalutation del reservas de ferro per medio de sectiones medullari. Determinationes del ferro de plasma, non supplementate per altere methodos, esseva de pauc valor in differentiar carentia de ferro ab altere anemias. Determinationes de ferro de plasma e del capacitate ferro-ligante esseva medios fidel pro le diagnose de carentia de ferro solmente in casos in que le hemoglobina amontava a minus que 9 g pro cento. In patientes con nivellos de hemoglobina de plus que 9 g pro cento, studios del contento de ferro e del capacitate de ligar ferro in le plasma esseva multo minus digne de confidentia como medios pro le differentiation inter carentia de ferro e altere formas de anemia. Le correlation del curva de tolerantia de ferro con le reservas de ferro esseva si imperfecte que le test de tolerantia de ferro debe esser considerate como disproviste de valor in le determination del reservas de ferro. Le clearance plasmatic e le utilisation erythrocytic de ferro radioactive non esseva sufficientemente afficite per le magnitude del

reservas de ferro pro render lor determination utilisabile como technica diagnostic in casos de leve carentia de ferro.

Esseva concludite que in le diagnose de leve grados de anemia a carentia de ferro e de depletion de ferro sin anemia, solmente le determination del ferro in le medulla ossee pote esser considerate como un methodo digne de confidentia.

BIBLIOGRAPHY

1. Beutler, E.: The clinical evaluation of iron stores, New England J. Med. **256**: 692–697, 1957.
2. Rath, C. E., and Finch, C. A.: Sternal marrow hemosiderin, J. Lab. and Clin. Med. **33**: 81–86, 1948.
3. Davidson, W. M., and Jennison, R. F.: The relationship between iron storage and anaemia, J. Clin. Path. **5**: 281–285, 1952.
4. Hutchison, H. E.: The significance of stainable iron in sternal marrow sections, Blood **8**: 236–248, 1953.
5. Stevens, A. R., Jr., Coleman, D. H., and Finch, C. A.: Iron metabolism: clinical evaluation of iron stores, Ann. Int. Med. **38**: 199–205, 1953.
6. Beutler, E., Drennan, W., and Block, M.: The bone marrow and liver in iron-deficiency anemia, J. Lab. and Clin. Med. **43**: 427–439, 1954.
7. Pratt, P. T., and Johnson, M. E.: Marrow iron stores in anemia, Arch. Int. Med. 93: 725–730, 1954.
8. Wallerstein, R. O.: Bone marrow hemosiderin in infants and children, J. Am. M. Women's A. **9**: 149–150, 1954.
9. Vries, A., and Izak, G.: Variations du taux de l'hémosidérine dans la moelle osseuse dans différentes conditions hématologiques, Rev. d'hémat. **10**: 657–664, 1956.
10. Kaplan, E., Zuelzer, W. W., and Mouriquand, C.: Sideroblasts. A study of stainable nonhemoglobin iron in marrow normoblasts, Blood **9**: 203–213, 1954.
11. Laurell, C. B.: Studies on the transportation of metabolism of iron in the body, Acta physiol. Scandinav. **14**: Supp. 46, 1947.
12. Rath, C. G., and Finch, C. A.: Chemical, clinical, and immunological studies on the products of human plasma fractionation. XXXVIII. Serum iron transport. Measurement of iron-binding capacity of serum in man, J. Clin. Investigation **28**: 79–85, 1949.
13. Cartwright, G. E., and Wintrobe, M. M.: Chemical, clinical, and immunological studies on the products of human plasma fractionation. XXXIX. The anemia of infection studies on the iron-binding capacity of serum, J. Clin. Investigation **28**: 86–98, 1949.
14. Jasinski, B.: Resorbtionstypen nach peroralen Eisenbelastung mit Ferronicum, Schweiz. med. Wchnschr. **80**: 59–62, 1950.
15. Thedering, F., Jr.: Diagnose und Behandlung des larvierten Eisenmangels, Med. Klin. **50**: 1463–1467, 1950.
16. Goldeck, H., Remy, D., and Labhard, H.: Eisenmangel und Schwangerschaft, Deutsche med. Wchnschr. **79**: 211–212, 1954.
17. Bothwell, T. H., Callender, S., Mallett, B., and Witts, L. J.: The study of erythropoiesis using tracer quantities of radioactive iron, Brit. J. Haemat. **2**: 1–16, 1956.
18. Beutler, E.: Unpublished observations.
19. Stevens, A. K.: The mechanism and treatment of iron deficiency anemia, Arch. Int. Med. **96**: 550–554, 1956.
20. Barkan, G., and Walker, B. S.: Determination of serum iron and pseudohemoglobin iron with o-phenanthroline, J. Biol. Chem. **135**: 37–42, 1940.
21. Weinstein, I. M., and Beutler, E.: The use of Cr^{51} and Fe^{59} in a combined procedure to study erythrocyte production and destruction in normal human subjects and in patients with hemolytic or aplastic anemia, J. Lab. and Clin. Med. **45**: 616–622, 1955.

22. Bothwell, T. H., Hurtado, A. V., Donohue, D. M., and Finch, C. A.: Erythrokinetics. IV. The plasma iron turnover as a measure of erythropoiesis, Blood **12**: 409–427, 1957.
23. Finch, S. C., and Finch, D. A.: Idiopathic hemochromatosis, an iron storage disease. A. Iron metabolism in hemochromatosis, Medicine **34**: 381–430, 1955.
24. Douglas, A. S., and Dacie, J. V.: The incidence and significance of iron-containing granules in human erythrocytes and their precursors, J. Clin. Path. **6**: 307–313, 1953.
25. Morse, W. I., and Read, H. C.: Stainable iron in marrow cells and erythrocytes in anemia, Canad. Serv. M. J. **10**: 244–252, 1954.
26. Smith, C. H., Sisson, T. R. C., Floyd, W. H., Jr., and Siegal, S.: Serum iron and iron-binding capacity of the serum in children with severe Mediterranean (Cooley's) anemia, Pediatrics **5**: 799–807, 1950.
27. Wallerstein, R. O., and Aggeler, P. M.: Differentiating between thalassemia minor and iron deficiency, California Med. **84**: 176–179, 1956.
28. Waldenstrom, J.: Iron and epithelium. Some clinical observations, Acta med. Scandinav. Suppl. **90**: 380–397, 1938.
29. Jasinski, B.: Zur Frage der nicht- und der leicht anamischen Eisenmangelkrankheit, Praxis **38**: 811–816, 1950.

LESSONS FROM SERUM CHOLESTEROL STUDIES IN JAPAN, HAWAII AND LOS ANGELES*†

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Two years ago, at the meeting of the College in Philadelphia, we reported some of our findings in South Africa. These data were in conformity with the hypothesis that dietary fat is an important element in the remarkable differences between populations in the frequency of coronary heart disease.[1, 2]

It is now possible to report related findings in Japan and on Japanese in Hawaii and in Los Angeles.

The basic question under investigation is this: What causes the striking differences in the frequency of coronary heart disease in different populations? Research on this question, and related studies on the cholesterol lipoprotein system in the blood in controlled dietary experiments on man, have led to a hypothesis about the influence of dietary fats on the development of coronary heart disease. The hypothesis may be stated as follows:

1. The etiology of coronary heart disease is multiple, but the development of the majority of cases in our society is dominated by the long-time effect of a rich fatty diet and an endless succession of fat-loading meals.

2. One effect of our kind of high fat diet is hypercholesterolemia, and this is so universal among us that our so-called cholesterol norms are simply standards for preclinical coronary disease. Hypercholesterolemia promotes atherosclerosis.

3. Fatty meals induce changes in the coagulability and other characteristics of the blood that favor thrombosis and inhibit fibrinolysis.[3, 4, 5]

4. Food fats differ in their effect on the blood cholesterol, but those fats most favored and abundant in our own diet are more powerful in promoting hypercholesterolemia than are those food oils that have a neutral or oppos-

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ing effect. It takes about 2 gm. of linoleic acid to offset the effect of 1 gm. of palmitic or stearic acid.[6]

5. The thrombus-inducing factor or factors in food fats and oils cannot be attributed to the fatty acids as such, and corn oil is no better than beef fat in this respect.[5]

TABLE 1

Mortality Rates, per 100,000 of Given Age, for Men Aged 50 to 54 in 1953–54 (From Official Vital Statistics)

Cause	U.S.A.	Japan
1. All causes	1,189	1,163
2. Infective and parasitic diseases	39	177
3. All neoplasms	206	236
4. Coronary (Internat. List Nos. 420, 422)	445	33
5. Hypertension plus Cerebrovascular Lesions	115	251
6. All violence	124	112
7. Ill defined and not known	13	35

6. Obesity, physical inactivity and economic privilege do not, of themselves, necessarily lead to the development of coronary heart disease.[7, 8, 9] But the rich man's table is apt to offer only a choice among rich foods. In America now we are all economically privileged, we are protected from exercise, the fat of the land is ours, and we try to fight obesity by cutting out bread and potatoes. So almost all Americans now eat high fat diets; we are pleased to be able to afford the most expensive fats, that is, the most highly

TABLE 2

Comparison between Mortality Rates from Vital Statistics and Calculated from a Nationwide Morbidity Survey with Follow-Up on Lethality (Data from Kusukawa, 1956)

Cause	Lethal Rate per 100 Cases	Death Rate From Morbidity +Lethality	Death Rate From Vital Statistics
All morbidity	0.7	758	970
I. Infective and parasitic	1.2	115	147
VII. Circulatory diseases	2.9	58	64
XVII. All violence	0.5	29	34

saturated fats. Our situation is at the opposite extreme from that in Japan, where the diet is remarkably low in fats. Table 1 summarizes some vital statistics.

Of all large countries with detailed vital statistics, Japan reports the lowest mortality rate from coronary heart disease. Mortality rates from tuberculosis, cancer and cerebrovascular lesions are known to be high, yet the total mortality of middle aged men is somewhat less than our own. This lends credibility to the remarkable discrepancy in coronary mortality shown here.

TABLE 3

Experience with Japanese Patients of Three Private Clinics in Japan and Three in Hawaii during the Month of March, 1956 (Data collected by Dr. B. Bronte-Stewart)

Place	Number of Patients Seen		
	Total	Hypertensive	Coronary
Honolulu	433	50	34
Fukuoka	381	38	1

Moreover, as table 2 shows, a large scale morbidity survey in Japan, with follow-up to find lethality, yielded reasonable agreement on the mortality rate for International List (1948), Category VII, Circulatory Diseases.[10] In spite of much rheumatic and hypertensive heart disease in Japan, the total mortality from circulatory diseases is low.

Such facts called for an extensive research program on the Japanese in Japan, in Hawaii and in California. Table 3 summarizes findings in private medical practice on Japanese in Fukuoka, Japan, and in Honolulu. This experience of the private practitioners in Hawaii and in Japan is no different from that in the big public hospitals. Dr. Paul White and other internists who checked these hospitals will testify that coronary heart disease is fairly common among Japanese in Hawaii but very rare in Japan. Hypertension is common in both regions.

Figure 1 summarizes findings on the frequency of severe atherosclerosis in consecutive autopsies, deaths from all causes. We checked the compara-

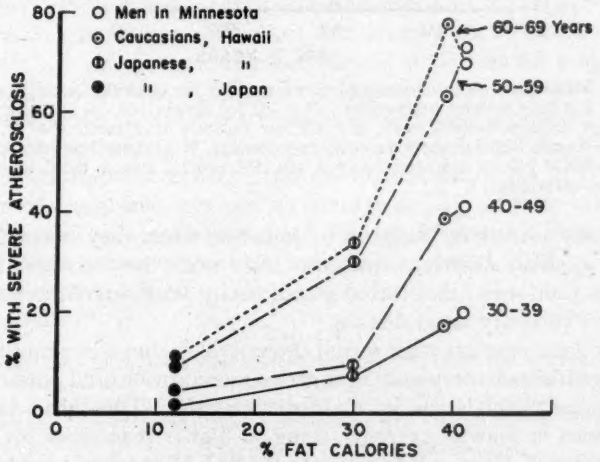

FIG. 1. Percentage of consecutive autopsies, deaths from all causes, showing severe (Mayo Clinic grades 3 and 4) coronary atherosclerosis among men aged 30 to 69 years, in Minnesota (400 autopsies), in Hawaii (141 Japanese, 270 Caucasians), and in Fukuoka, Japan (400 autopsies). The average percentage of calories provided by fats in the diet for these populations is given on the abscissa.

bility of methods and grading. Minnesotans and Caucasians in Hawaii are almost identical, but the incidence of severe atherosclerosis in Japanese men in Kyushu is only a tenth as great. Japanese men in Hawaii are intermediate. We lack comparable data for Japanese in California, but at least it is known that coronary heart disease is their leading cause of death, and the representation of the disease at the Los Angeles Japanese Hospital and in private practice there is much the same as for the Caucasians in California. According to vital statistics, Japanese in California appear to be no different from other Californians; coronary heart disease is their leading cause of death.

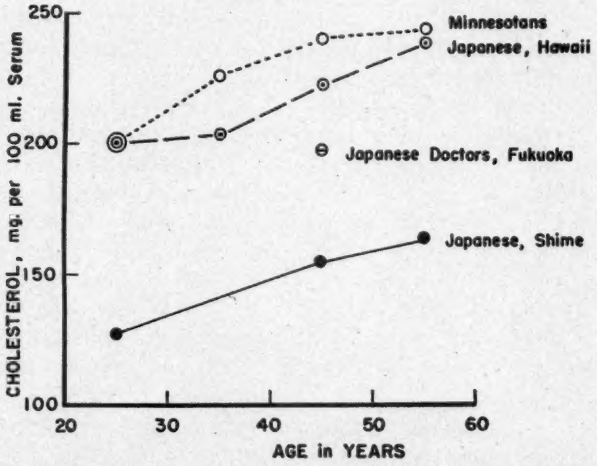

FIG. 2. Mean serum total cholesterol concentrations for clinically healthy men engaged in sedentary and light activity occupations. N = 153 for Shime (49, 54, and 50 men in third, fifth and sixth decades, respectively), N = 122 for Japanese in Hawaii (34, 27, 33, and 28 men in third, fourth, fifth and sixth decades, respectively), N = 52 for Fukuoka doctors (ages 40 to 49), and N = 940 for Minnesotans (163, 186, 234, and 357 men in third, fourth, fifth and sixth decades, respectively).

Obviously something happens to Japanese when they move to Hawaii and begin to adopt American customs. And when they become fully Americanized in California, this includes conformity with our American pattern of excessive coronary heart disease.

Figure 2 summarizes total serum cholesterol findings in clinically healthy men engaged in sedentary and light activity occupations, all studied in 1956 with the same methods and by the same analysts. The values for the 110 Japanese men in Hawaii average 76 mg.% higher than those for their 153 counterparts in Kyushu, while those for the 831 Minnesotans are higher still.

These 1956 measurements probably represent the situation during a number of preceding years among Minnesotans and men in Japan, but there is some question about the former dietary situation in Hawaii, where Ameri-

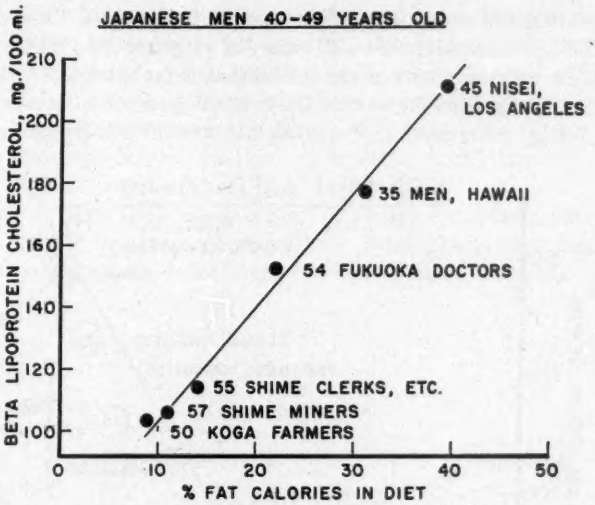

FIG. 3. Mean percentage of calories provided by all fats in the diet and concentration of beta lipoprotein-cholesterol in the serum of Japanese men aged 40 to 49 in Japan, in Hawaii, and in Los Angeles.

canization of the resident Japanese has progressed rapidly in the last few years, especially among the younger men. Note the high value for the youngest group in Hawaii; these young men are now just as addicted to hamburgers and ice cream as are the local Caucasians.

Figure 3 summarizes cholesterol and dietary data for men aged 40 through 49. It was possible to make dietary studies on all subjects. The same chief dietitian, Mrs. S. Miyamoto, supervised the work in Hawaii and Los Angeles, while in Kyushu a team of 10 dietitians conducted the household inventory and purchase surveys. Fats provided less than 10% of total calories for the farmers at Koga, and the highest fat intake in Kyushu was that of the 54 physicians, who got an average of 22% of their calories from fats. In Hawaii the Japanese men of this age averaged a little over 30% fat calories, and in Los Angeles the average was almost 40%. Serum cholesterol was linearly related.

TABLE 4

Mean Alpha and Beta Lipoprotein-Cholesterol Concentrations in the Blood Serum of Sedentary Japanese Men, aged 40 to 49, Matched as to Relative Fatness; Also Average Percentage of Calories Provided by Fats in the Diets of These Same Men

Place	% Fat Calories	Cholesterol, mg.%	
		α	β
Shime	13	40.3	120.3
Honolulu	32	40.4	183.0
Los Angeles	40	35.2	212.7

This relationship is not dependent upon differences in total calories or obesity. Table 4 compares 40-to-49 year old Japanese men matched in relative obesity by measurements of the subcutaneous fat thickness with skinfold calipers. This table also shows that the total cholesterol differences are fully accounted for by differences in the concentration of beta lipoprotein choles-

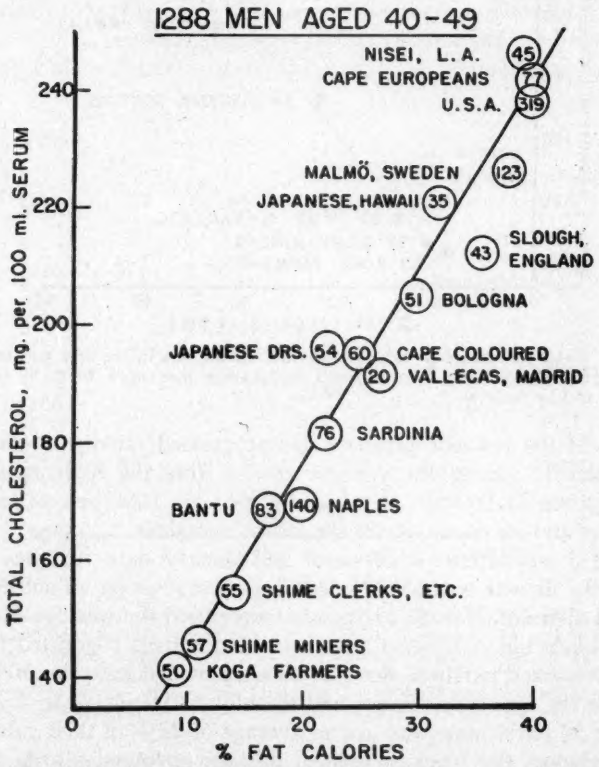

FIG. 4. Mean percentage of calories provided by all fats in the diet and concentration of total cholesterol in the serum of 1,288 clinically healthy men aged 40 to 49 in gainful employ in the United States, (Minnesota railroad clerks, switchmen, dispatchers, Minneapolis firemen, Los Angeles Caucasians), Malmö, Sweden (shipyard workers, firemen, clerks, engineers, foremen), Bologna (policemen, factory workers, businessmen), Sardinia (policemen, firemen, coal miners), Naples (firemen, steelworkers, clerks), and in other groups as indicated. Numbers within the circles show the number of men in each group.

terol. The lipoproteins were separated by paper electrophoresis, and cholesterol was measured in separate fractions. As in our other population studies, alpha lipoprotein cholesterol does not vary beyond the range of about 35 to 45 mg. per 100 ml.

These findings on Japanese are, as shown in figure 4, in conformity with the data on other racial groups. The dietary and cholesterol data suggest

no peculiarity of Japanese or Bantu or Americans or Italians, and so on. They all conform to the same pattern. Further, this graph shows no peculiarity of men doing heavy manual labor as contrasted with men in sedentary and light work. Heavy labor here is represented by the Japanese farmers at Koga and the miners at Shime, Bantu at Cape Town, the steel workers at Ilva near Naples, coal miners at Bacu Abis, Sardinia, and shipbuilders at Malmö, Sweden.

In Japan we were able to make a small dietary experiment, summarized in figure 5, on 18 Japanese coal miners.[11] Fifty grams of butter or margarine were isocalorically substituted for rice in their customary diet. In

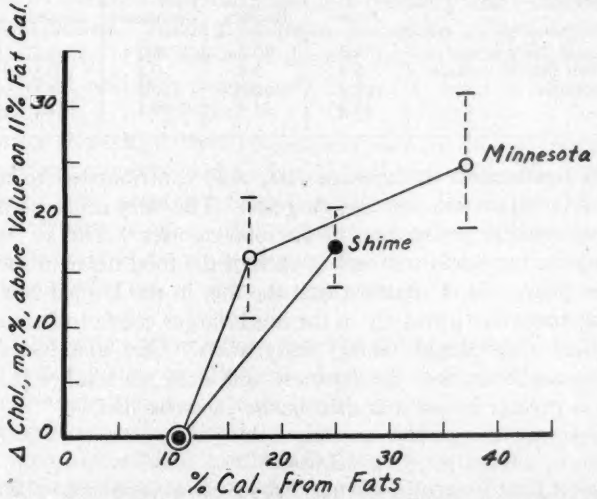

FIG. 5. Mean change in serum total cholesterol of Japanese coal miners at Shime and of Minnesota Hastings State Hospital men in response to isocaloric substitution of butterfat or margarine for carbohydrate in a low fat diet. Vertical broken lines show standard errors.

11 days there was a significant rise in the serum cholesterol, and this corresponded in magnitude to the results of similar experiments made on Minnesota men at the Hastings State Hospital. We conclude that the low cholesterol values of the Japanese in Japan is fully explained by the fat, or lack of it, in the diet.

There is, however, the question as to the kind of fat in the Japanese and the American diets. Table 5 summarizes fat calories according to source for the Japanese studied in Shime, Honolulu and Los Angeles, and for the Caucasian controls studied in parallel in Honolulu and in Los Angeles. Except in Los Angeles, the Japanese get a larger proportion of their calories from fish and marine invertebrates than do the Caucasians. All groups except the Japanese at Shime get most of their diet fats from meat, eggs, and dairy products, that is from relatively saturated fats.

In controlled dietary experiments we have found that fish oil, in spite of its extreme degree of unsaturation, does not have any remarkable cholesterol-lowering effect; it is about equivalent to cottonseed oil in this respect.[12] Calculations indicate, in fact, that more than the two double bonds in linoleic are without further effect on the blood cholesterol.

TABLE 5

Percentages of Total Calories in the Diet from Fats Classified as to Source; Clinically Healthy Men Studied in 1956

Source	Japanese			Caucasians	
	Shime	Honolulu	Los Angeles	Honolulu	Los Angeles
Meat, eggs and dairy products	3.3	20.2	28.1	33.7	28.0
Fish and other marine animals	5.9	1.4	0.8	0.8	0.5
Vegetable sources	2.8	10.2	10.2	6.7	13.9
Total	12.0	31.8	39.1	41.2	42.4

Table 6 summarizes the average fatty acid contributions to the diet in Kyushu and in Minnesota and Los Angeles. The fatty acids, as the glycerides, are expressed as percentages of the total calories. This is the result of summing up the fatty acid contents of each of the food items in the recorded food consumption. It is apparent that the diet in the United States differs from the Japanese diet primarily in the much larger content of saturated and mono-ethenoid (one double bond) fatty acids. Our diet contains much more linoleic acid than does the Japanese, and even the total of polyethenoid fatty acids is greater in our diet than in the Japanese diet.

TABLE 6

Percentages of Total Dietary Calories from Fatty Acids, as Glycerides, in Diets of Men Studied in Minnesota and Los Angeles and in Kyushu, Japan

Fatty Acids	U.S.A.	Kyushu
Saturated	17.6%	2.6%
Mono-ethenoid	17.3	4.7
Linoleic	4.6	2.6
Other poly-ethenoid	0.5	2.1
Total	40.0%	12.0%

This is, in fact, the general pattern of diets in most populations. As populations increase their fat consumption, they do so mainly by increasing their use of meat and dairy fats, but their intake of linoleic or so-called essential fatty acids also rises somewhat. The resulting rise in serum cholesterol is attributable to an increased intake of saturated fats and not to a decreased intake of unsaturated fats.

The relative influence of different fats on the serum cholesterol-lipoprotein system of man has been the subject of a major research program in

Minnesota for the last six years. Over 20,000 subject-days of controlled dietary experiments on man have recently been analyzed. The result is to show that 1 gm. of saturated fat requires about 2 gm. of linoleic acid to counter the effect on the serum cholesterol. This agrees with our population studies and the conclusion that in natural human diets the content of saturated fatty acids is dominant. Frying the hamburger steak in sunflower seed oil does not seem to be the solution.[12]

Conclusion

The low incidence of atherosclerosis and coronary heart disease in Japan is clearly established. Among Japanese, as among other peoples, the incidence of coronary heart disease is directly related to the average level of serum cholesterol, and it is unnecessary to invoke racial or other factors in explanation.

The serum cholesterol level in Japanese men is directly related to the percentage of calories provided by fats in the diet. The effect of the fats is dominated by the saturated fats of meats and dairy products. Among Japanese, as in most of the world's populations, when the diet is increased in fats, this increase is mainly accounted for by increasing consumption of the more saturated types of fats, as represented in beef, pork and dairy products.

These findings do not constitute proof of the hypothesis that dietary fat is a major factor in the development of coronary heart disease. But the findings are consistent, in detail, with the theory.

The theory is consistent not only with our findings in comparing Japan with the United States—it is consistent also with the results of our studies in North and South Italy, in South Africa, in England, in Spain, in Sweden and, most recently, in Finland. It is consistent with the findings of others in Guatemala, in Israel, in India, in Nigeria and in West Germany. So far, all investigations on populations subsisting on low-fat diets show such populations to be characterized by a low incidence of atherosclerosis and coronary heart disease and a low average level of cholesterol in the blood in comparison with populations who subsist on high fat diets. All populations known to have an incidence of the disease comparable to that in the United States or in Great Britain obtain at least a third of their calories in the form of fats in which fats from meats and dairy products make a large contribution.

Two exceptions to these rules have been claimed—the Eskimo and the Navajo Indian. On investigation, however, these "exceptions" prove to be based on faulty or absent information, and failure to realize that in both of these small populations the number of men of an age appropriate to the exhibition of coronary heart disease is extraordinarily small. The majority of Eskimos in modern times eat a diet considerably lower in fats than do

contemporary Americans, and the few primitive Eskimos who do eat a high fat diet (only slightly higher in fat calories than the diet in the United States) consume very little of the common meat and dairy fats characteristic of the United States and other regions where coronary heart disease is common. In any case, practically nothing is known about the frequency of coronary atherosclerosis and heart disease among Eskimos.

Study of the Navajo Indians does not support the suggestion that the Navajos eat the high fat diet typical of most Americans today, yet suffer no coronary heart disease. Navajo diets are not high in total fats and are very low in dairy fats. The average age of the Navajo population is far lower than that of the United States as a whole (about half of them are 15 years old or younger), and there are no reliable data on the frequency of atherosclerosis or coronary heart disease among them. Arteriosclerotic heart disease and myocardial infarction are not vanishingly rare, and the incidence seems to be roughly what would be expected with a diet of around 25% fat calories, including little or no butterfat. In other words, the Navajos apparently resemble the inhabitants of Sardinia or the Cape colored people of South Africa in these respects.

Summary

1. Studies on the diet, the serum cholesterol and the frequency of atherosclerosis and coronary heart disease have been made in Japanese in Japan, where coronary heart disease is rare, in Hawaii, where it is fairly common but less so than among local Caucasians, and in California, where the local Japanese are similar to the local Caucasians in regard to the frequency of the disease. In middle age, coronary heart disease is at least 10 times as common in the United States as in Japan.

2. In 475 Japanese the serum cholesterol concentration showed a linear relationship to the percentage of calories provided by fats in the diet from a low among farmers at Koga, and a slightly higher average among miners at Shime, Japan, to a high among Nisei in Los Angeles, who were not significantly different from local Caucasians in this respect. These differences (averaging 96 mg. per 100 ml. comparing 40-to-49 year old Koga farmers, eating less than 10% fat calories, with Los Angeles Nisei of the same age, eating 39% fat calories) were accounted for by beta lipoprotein cholesterol, the alpha fraction showing no significant variation. These differences are not accounted for by differences in climate, relative obesity, physical activity, the use of alcohol and tobacco, the concentration of protein in the diet or the intake of "essential" fatty acids.

3. The findings on the Japanese are consistent with the theory that an important factor in producing differences in the frequency of coronary heart disease in populations is the proportion of calories in the diet provided by fats, particularly the common saturated fats.

ACKNOWLEDGMENT

The results reported here could not have been obtained without able and generous assistance and coöperation. *In Japan:* Dr. Masakazu Yoshitomi, Dr. Nobuki Endo, Dr. Y. Noda, Dr. R. Kikuno, Dr. G. Hashimoto, Mr. S. Miwa, Mr. P. Ishida, Mrs. M. Yasutake, Miss T. Oka, Mrs. T. Tsutsumi, Mrs. T. Takimoto, and the Staff of the 1st Medical Clinic of Kyushu University and of the Shime Hospital. *In Hawaii:* Mr. and Mrs. Steve Chinen, Mr. K. Goto. *In Los Angeles:* Dr. John Denny, Dr. T. Watanabe, Dr. Ben Kondo, Dr. Ed Phillips, Dr. George Matsumo, Dr. Robert Stivelman, Mrs. Nedra Foster. Mrs. Shizuko H. Miyamoto supervised the dietary work both in Los Angeles and in Hawaii. Dr. Joseph T. Anderson supervised the cholesterol measurements in Minneapolis on serum samples sent from Japan, Hawaii and Los Angeles.

SUMMARIO IN INTERLINGUA

Esseva studiate le dieta, le cholesterol seral, e le frequentia de atherosclerose e morbo coronari in subjectos japonese (1) in Japon, ubi morbo cardiac coronari es rar, (2) in Hawai, ubi illo es satis commun inter le japoneses sed minus commun que inter le residente caucasianos, e (3) in California, ubi le residente japoneses es simile al residente caucasianos con respecto al frequentia del morbo. Inter individuos de etate medie, morbo cardiac coronari es al minus 10 vices plus commun in le Statos Unite que in Japon.

Determinationes del cholesterol seral in 475 masculos japonese de etates de inter 40 e 49 annos monstrava un relation linear inter le cholesterol seral e le procentage del calorias providite per grassias in le dieta. Tanto le nivello de cholesterol como etiam le procentage del calorias representate per grassias in le dieta esseva plus basse inter le fermeros de Koga, levemente plus alte inter le mineros de Shime, e le plus alte inter le nisei de Los Angeles (qui non differeva significativemente ab le caucasianos local in iste respecto). Iste differentias amontava a un valor medie de 96 mg de cholesterol per 100 ml quando fermeros de Koga, de etates de inter 40 e 49 annos e alimentate con dietas in que minus que 10 pro cento del calorias esseva fornite per grassias, esseva comparate con le nisei de Los Angeles, del mesme gruppo de etate sed con dietas in que 39 pro cento del calorias esseva fornite per grassia. Le differentias se concentrava in le fraction lipoproteinic beta. Le fraction alpha non monstrava un variation significative. Le differentias del cholesterol non se explica per differentias de climate, del obesitate relative, del activitate physic, del uso de alcohol e tabaco, del concentration de proteina in le dieta, o del ingestion de acidos grasse "essential."

Iste constatationes in subjectos japonese es de accordo con le theoria que un importante factor in le production del differentias del numero de casos de morbo cardiac coronari in varie populationes es le proportion de calorias dietari providite per grassias, specialmente le commun grassias saturate.

Le constatationes es de accordo con le resultatos de nostre previe studios in Nord- e Sud-Italia, in Sud-Africa, in Anglaterra, in Espania, in Sveda, e, le plus recentemente, in Finlandia.

BIBLIOGRAPHY

1. (a) Keys, A.: The cholesterol problem, Voeding (Amsterdam) **13**: 539–555, 1952.
   (b) Keys, A.: Human atherosclerosis and the diet, Circulation **5**: 115–118, 1952.
   (c) Keys, A.: Atherosclerosis: a problem in newer public health, J. Mt. Sinai Hosp. **20**: 118–139, 1953–54.
   (d) Keys, A.: Prediction and possible prevention of coronary disease, Am. J. Pub. Health **43**: 1399–1407, 1953.
2. Keys, A.: The diet and the development of coronary heart disease, J. Chron. Dis. **4**: 364–380, 1956.

3. Buzina, R., and Keys, A.: Blood coagulation after a fat meal, Circulation **14**: 854–858, 1956.
4. Keys, A., Buzina, R., Grande, F., and Anderson, J. T.: Effects of meals of different fats on blood coagulation, Circulation **15**: 274–279, 1957.
5. Greig, H. B. W.: Inhibition of fibrinolysis by alimentary lipaemia, Lancet **2**: 16–18 (July 7) 1956.
6. Keys, A., Anderson, J. T., and Grande, F.: "Essential" fatty acids, degree of unsaturation, and the effect of corn (maize) oil on the serum-cholesterol level in man, Lancet **1**: 66–68 (Jan. 12) 1957.
7. Keys, A.: Obesity and degenerative heart disease, Am. J. Pub. Health **44**: 864–871, 1954.
8. Brozek, J., and Keys, A.: Overweight, obesity, and coronary heart disease, Geriatrics **12**: 79–87, 1957.
9. Keys, A., Anderson, J. T., Aresu, M., Biörck, G., Brock, J. F., Bronte-Stewart, B., Fidanza, F., Keys, M. H., Malmros, H., Poppi, A., Posteli, T., Swahn, B., and del Vecchio, A.: Physical activity and the diet in populations differing in serum-cholesterol, J. Clin. Investigation **35**: 1173–1181, 1956.
10. Kusukawa, A.: Statistical findings on the incidence of coronary heart disease in Japan, *in* World trends in cardiology, edited by A. Keys and P. D. White, 1956, Hoeber-Harper, New York, pp. 159–163.
11. Keys, A., Kimura, N., Kusukawa, A., and Yoshitomi, M.: Serum cholesterol in Japanese coal miners: a dietary experiment, Am. J. Clin. Nutrition **5**: 245–250, 1957.
12. Keys, A., Anderson, J. T., and Grande, F.: Serum-cholesterol response to dietary fat, Lancet **1**: 787 (Apr. 13) 1957.

ESTROGEN REPLACEMENT THERAPY IN WOMEN WITH CORONARY ATHEROSCLEROSIS *

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Introduction

Coronary heart disease is rarely encountered in premenopausal women.[1, 2] However, postmenopausally a sharp rise in the incidence of this disease has been reported in the sixth decade of life,[3, 4] and by the seventh decade the incidence approaches that of men. A fundamental biochemical alteration associated with the menopause is the substantial decrease of ovarian estrogen production, as measured by urinary estrogen levels.[5] Alterations of the serum lipids coincident with this low estrogen production have been reported. These include increases of serum cholesterol,[6, 7] of cholesterol-phospholipid ratio,[8, 9] and of β-/α-lipoprotein-cholesterol ratio.[9] The frequent association of these abnormalities with coronary atherosclerosis has been reported by Barr.[9] Estrogens revert the abnormal serum lipids toward normal levels in both animals and human subjects.[9, 10, 11, 12] Furthermore, autopsy studies suggest a decreased incidence and severity of atherosclerosis in patients receiving estrogens during life, and in hyperestrogenic states.[13, 14] The demonstration by Marmorston et al.[15] of decreased urinary estrogen excretion in women with myocardial infarction is further evidence that diminished estrogens are associated with coronary atherosclerosis.

Despite the evidence cited, no studies on the effects of estrogen administration on serum lipids in women have been published since those of Eilert, which involved short-term trials in 12 women with coronary heart disease.[16] Reports of estrogen administration to male patients have all stressed the undesirable "feminizing" side-effects. In women, on the other hand, these feminizing effects are desirable. Consequently, a study of the effects of long-term estrogen therapy on the serum lipids in postmenopausal women seemed warranted. This is an initial report of (1) the serum lipid patterns of normal young women and postmenopausal women, (2) the results of estrogen therapy in women with coronary heart disease, and (3) estrogen prophylaxis as a possible means to control the elevated serum lipids in clinically normal postmenopausal women.

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Material and Methods

Serum lipid studies and clinical evaluations were carried out on 22 normal young women in the third decade of life, and on 113 normal postmenopausal women between the ages of 45 and 65.

In the therapeutic approach to coronary atherosclerosis in women, 35 patients with angina pectoris or myocardial infarction were selected for study. It had been shown previously in men with coronary atherosclerosis that 10 mg. of oral mixed conjugated estrogens (Premarin) daily have a favorable effect on serum lipids, and no deleterious effects on adrenal cortical or thyroid functions.[11] For this reason, the women in this group received either 5 or 10 mg. of Premarin after control studies. Because this dosage would often cause uterine bleeding, only women who previously had

Table 1

Comparative Serum Lipid Values in Young and in Postmenopausal Women

Group	Number of Women	Cholesterol, Mg. %	Phospholipids, Mg. %	C/P Ratio	β^-/α^- Lipoprotein-Cholesterol Ratio
Normal Young ♀ Age: 20–30	22	189±4.6	193±6.1	0.99±0.040	2.4±0.31
Normal postmenopausal ♀ Age: 45–65	113	262±4.1	226±3.3	1.16±0.015	3.4±0.12
Significance of difference		t=7.54 P<0.01	t=4.27 P<0.01	t=4.55 P<0.01	t=3.33 P<0.01

had a hysterectomy for gynecologic reasons were chosen. Clinical and laboratory evaluations were performed at one, three, six and 12 months of therapy.

A group of 58 postmenopausal women without clinical evidence of atherosclerosis was selected for the third portion of this study, the purpose of which was the determination of the optimal dose of estrogen to revert the blood lipids to levels characteristic of normal young women, who rarely have atherosclerosis. To do this, the effect of stepwise increases of estrogen dosage every three months on the serum lipids was observed. The initial dose was 1.25 mg. of Premarin daily. The dosage was then increased to 2.5 mg. Because doses above 1.25 mg. may frequently cause uterine bleeding, again only previously hysterectomized patients were studied at higher dosages. Additional investigation, now in progress, is required to determine whether an optimal dose produces disturbing estrogen bleeding in women with intact uteri.

Total serum cholesterol and phospholipids were determined by methods previously described.[11] The cholesterol-phospholipid ratio was derived from these results. Separation of β-lipoproteins was carried out by ultracentrifugal flotation at a protein-free solvent density of 1.063,[17] with sub-

TABLE 2

Serum Lipid Alterations in Women with Coronary Heart Disease: Comparison with Normal Women

Group	Number of Women	Average Age	Cholesterol, Mg. %	Phospholipids, Mg. %	C/P Ratio	β^-/α^- Lipoprotein-Cholesterol Ratio
Women with C.A.D.	58	55	270±7.5	225±5.6	1.20±0.020	4.1±0.19
Normal postmenopausal women	113	55	262±4.1	226±3.3	1.16±0.015	3.4±0.12
Significance of difference			t=1.03 Not Significant	Not Significant	t=1.62 Not Significant	t=3.27 P<0.01

sequent analysis of the cholesterol content of both the floated low density layer (β-lipoproteins) and the sedimented layer (including the α-lipoproteins). The β-/α-lipoprotein-cholesterol ratio was calculated from the cholesterol content of the two fractions. Recovery of total serum cholesterol was 97 ± 5% by this method. Vaginal smears, stained by the Papanicolaou technic, were taken prior to therapy and frequently thereafter in order to assess the effect of estrogen therapy.

RESULTS AND DISCUSSION

Table 1 shows that there are significant differences in the serum lipid patterns between young women and postmenopausal women. In the latter group, the elevation of serum total cholesterol is greater than that of the serum phospholipids, resulting in an increased cholesterol-phospholipid ratio.

TABLE 3

Clinical Data on Women with Coronary Heart Disease Treated with 5 or 10 mg. of Premarin Daily

	Number		Per Cent
Patients studied	35		
Average age	55 yrs.	Range 42–65	
Average duration of treatment	14 months	Range 2–31 months	
Oophorectomized prior to age 45	11		31
Hypertension (B.P.>150/100)	25		71
Borderline hypertension (140/90<B.P.<150/100)	5		14
Type of disease			
Angina pectoris (only)	21		60
Myocardial infarct	14		40
Diabetes	1		
Deaths during therapy	2		
D.B. after 17 mos.			
A.M. after 2 mos.			

The ratio of cholesterol in the β-lipoprotein fraction to that in the α-fraction is also significantly increased.

To determine whether specific serum lipid abnormalities are characteristic of women with coronary heart disease, the data of 58 patients were compared with those of 113 normal postmenopausal individuals (table 2). The mean serum total cholesterol and cholesterol-phospholipid ratio of the women patients were not significantly different from those of the normal women, but there was a highly significant increase of the β-/α-lipoprotein-cholesterol ratio in the coronary group. However, it cannot be inferred that a high β-/α-lipoprotein-cholesterol ratio has any predictive value in the normal population without more extensive long-term studies.

The clinical status of the 35 women with coronary atherosclerosis who received estrogen therapy is shown in table 3. Five or 10 mg. of oral Premarin were administered daily for an average of 14 months. It is noteworthy that 11 of these patients had been oophorectomized at a relatively young age. This raises the question of the role of premature estrogen deprivation in the pathogenesis of atherosclerosis in these women. The incidence of definite hypertension was 71%, comparable to that reported by others.[4] All of the patients tolerated these high doses without nausea or vomiting. Although breast tenderness was noted in 74%, this was transitory, lasting only two to six months. The most disturbing side-effects, occasionally requiring a decrease of estrogen dosage, were the recurrence of migraine in 21% of the patients and nocturnal leg cramps in 11%. No malignant cells have been observed in Papanicolaou smears in patients in whom the cervix was still present, with possible remaining endometrial tissue.

TABLE 4

Response of Serum Lipids to 5 or 10 mg. of Premarin Daily in 30 Women with Coronary Heart Disease

	Cholesterol, Mg. %	Phospholipids, Mg. %	C/P Ratio	β-/α- Lipoprotein-Cholesterol Ratio
Control level	266±9.6	222±8.1	1.21±0.027	4.2±0.27
Change from control	−28±7.8	+36±6.6	−0.29±0.032	−35±5.0%
3 mo. therapy (Level Achieved)	(238)	(258)	(0.92)	(2.7)
Significance of change	t=3.59 P<0.01	t=5.46 P<0.01	t=9.06 P<0.01	t=7.00 P<0.01

Table 4 depicts the dramatic response of the various serum lipid parameters after three months of therapy in 30 of this group of patients. Since no statistical differences were seen between the 5 and 10 mg. dosage groups, these results were combined. The serum lipid changes were seen as early as one month, and persisted throughout the treatment period. The resultant

cholesterol-phospholipid and β-/α-lipoprotein-cholesterol ratios (0.92 and 2.7, respectively) compared favorably with those of normal young women (0.99 and 2.4). All of these changes were significant below the 1% level of probability. Additional patients are being added to this group as they come under observation, and longevity studies will eventually be available for comparison with a control, untreated group.

Fifty-nine women without clinical atherosclerosis were placed on 1.25 mg. of Premarin daily for three months. Of the 16 with intact uteri, five had uterine bleeding. A recurrence of migraine in one individual and the

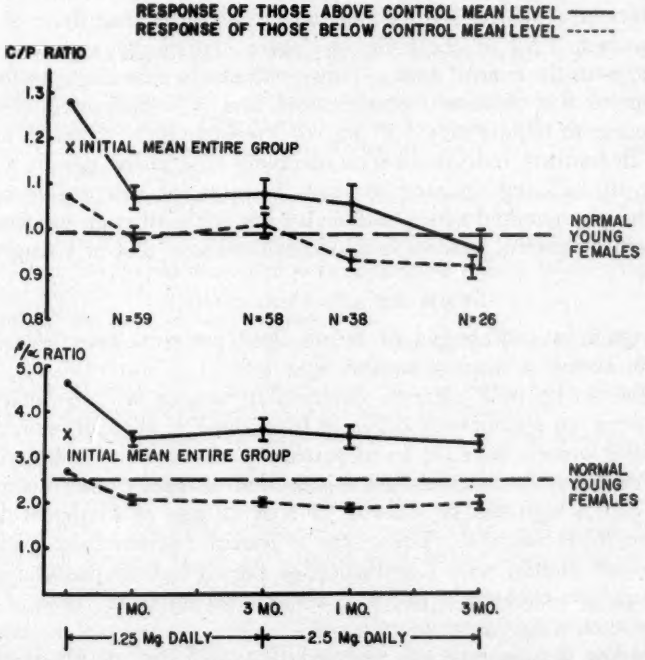

FIG. 1. Response of serum lipids to Premarin in women, subdivided into those with "better" and those with "worse" initial lipid values.

development of temporary breast tenderness in three were the only other complications. In 38 hysterectomized individuals the dosage was then increased to 2.5 mg. for an additional three months. At this dosage breast tenderness was more often seen (64%); migraine recurred in only two individuals, and nocturnal leg cramps were infrequent, occurring in only one. Since the number of individuals increased to 5 and 10 mg. dosages is as yet too small for statistical analysis, these results will not be discussed. The mean cholesterol-phospholipid and β-/α-lipoprotein-cholesterol ratios in this group were 1.18 and 3.5, respectively, during the control period. A sig-

nificant difference in response to the same dosage was noted in those individuals whose control ratios were either higher or lower than the above mean levels. The mean control cholesterol-phospholipid ratio of the lower group (1.07), despite its proximity to that of the normal young women (0.99), was statistically higher ($P = .01$). The mean control β-/α-lipoprotein-cholesterol ratio, however, was not significantly different. The mean control cholesterol-phospholipid ratio of the higher group was 1.28; the β-/α-lipoprotein-cholesterol ratio, 4.6. The bimodal response made necessary the separation of the data shown in figure 1. In the group with initially low cholesterol-phospholipid and β-/α-lipoprotein-cholesterol ratios, 1.25 mg. were sufficient to achieve levels comparable to or better than those of normal young women. All of these changes were statistically significant when compared with the control data. Thus, individuals with slight to moderate elevations of the cholesterol-phospholipid and β-/α-lipoprotein-cholesterol ratios appear to require only 1.25 mg. of Premarin daily to attain adequate levels. In contrast, individuals with markedly high ratios, despite a greater response to 1.25 mg., require at least 2.5 mg. for comparable resultant cholesterol-phospholipid ratios, although even at this dosage the final β-/α-lipoprotein-cholesterol ratio remains somewhat above that of young women.

Summary and Conclusions

1. Significant differences of serum lipid patterns have been demonstrated in normal women of various ages.

2. The serum lipid patterns observed in women with coronary heart disease were not significantly different from those of clinically normal postmenopausal women, save for an increased β-/α-lipoprotein-cholesterol ratio.

3. Previously hysterectomized women with coronary heart disease were treated with a high dosage schedule of 5 or 10 mg. of Premarin daily for from two to 31 months. There was a dramatic serum lipid response as early as one month, with a reduction of the cholesterol-phospholipid and β-/α-lipoprotein-cholesterol ratios to levels comparable to those of normal young women within three months.

4. A low dosage schedule revealed that 1.25 mg. of Premarin daily adequately reduced the cholesterol-phospholipid and β-/α-lipoprotein-cholesterol ratios in women whose ratios were initially below the group mean. In women with ratios initially above the group mean, this dosage failed to achieve a comparable level. An increase of dosage to 2.5 mg. daily resulted in a satisfactory lowering of the cholesterol-phospholipid ratio, although the β-/α-lipoprotein-cholesterol ratio remained somewhat elevated.

5. Complications of estrogen therapy have been noted, but these were not serious. They included breast tenderness, recurrence of migraine and nocturnal leg muscle cramps. Breast tenderness was temporary, but either migraine or leg cramps, when sufficiently severe, made necessary the cessation or decrease of estrogen dosage.

SUMMARIO IN INTERLINGUA

In le studio hic reportate, alterationes del grassia de sanguine esseva investigate in feminas post-menopausal, tanto in stato de bon sanitate como etiam con coronari morbo cardiac. Proque anormalitates del grassia de sanguine esseva trovate in ambe gruppos, hormones de sexo feminin (estrogenos) esseva administrate a certe seligite individuos, con le resultato que le grassias de sanguine retornava a nivellos simile a illos incontrate in juvene feminas qui quasi nunquam experientia le disveloppamento de coronari morbo cardiac. Ha essite initiate un plano pro studiar iste feminas durante plure annos con le objectivo de determinar si le tractamento exerce un effecto favorabile super le disveloppamento de morbo coronari.

BIBLIOGRAPHY

1. Glendy, R. E., Levine, S. A., and White, P. D.: Coronary disease in youth: comparison of 100 patients under 40 with 300 persons past 80, J. A. M. A. **109**: 1775, 1937.
2. Gertler, M. M., White, P. D., and others: Coronary heart disease in young adults. A multidisciplinary study, 1954, Harvard University Press, Cambridge.
3. James, T. N., Post, H. W., and Smith, F. J.: Myocardial infarction in women, Ann. Int. Med. **43**: 153, 1955.
4. Weinreb, H. L., German, E., and Rosenberg, B.: A study of myocardial infarction in women, Ann. Int. Med. **46**: 285, 1957.
5. Pincus, G., Dorfman, R. I., Romanoff, L. P., Rubin, B. L., Bloch, E., Carlo, J., and Freeman, H.: Steroid metabolism in aging men and women, Recent Progress Hormone Research **11**: 307, 1955.
6. Dawber, T. R.: Personal communication, 1957.
7. Jones, H. B., Gofman, J. W., Lindgren, F. T., Lyon, T. P., Graham, D. M., Strisower, B., and Nichols, A. V.: Lipoproteins in atherosclerosis, Am. J. Med. **11**: 358, 1951.
8. Adlersberg, D., Schaefer, L. E., Steinberg, A. G., and Wang, C.-I.: Age, sex, serum lipids, and coronary atherosclerosis, J. A. M. A. **162**: 619, 1956.
9. Barr, D. P.: Some chemical factors in the pathogenesis of atherosclerosis, Circulation **8**: 641, 1953.
10. Katz, L. N., and Stamler, J.: Experimental atherosclerosis, 1953, Charles C. Thomas, Springfield, Illinois.
11. Robinson, R. W., Higano, N., Cohen, W. D., Sniffen, R. C., and Sherer, J. W., Jr.: Effects of estrogen therapy on hormonal functions and serum lipids in men with coronary atherosclerosis, Circulation **14**: 365, 1956.
12. Oliver, M. F., and Boyd, G. S.: The influence of the sex hormones on the circulating lipids and lipoproteins in coronary sclerosis, Circulation **13**: 82, 1956.
13. Wuest, J. H., Jr., Dry, T. J., and Edwards, J. E.: The degree of coronary atherosclerosis in bilaterally oophorectomized women, Circulation **7**: 801, 1953.
14. Rivin, A. U., and Dimitroff, S. P.: The incidence and severity of atherosclerosis in estrogen-treated males, and in females with a hypoestrogenic or a hyperestrogenic state, Circulation **9**: 533, 1954.
15. Marmorston, J., Hoffman, O., Sobel, H., and Starr, P.: Urinary estrogen and serum protein-bound iodine levels in a group of post-menopausal women with and without myocardial infarction, Proceedings of Symposium on Arteriosclerosis, Minneapolis, Minnesota, 1955.
16. Eilert, M. L.: The effect of estrogens upon the partition of the serum lipids in female patients, Am. Heart J. **38**: 472, 1949.
17. DeLalla, O. F., and Gofman, J. W.: Ultracentrifugal analysis of serum lipoproteins, *in* Methods of biochemical analysis, 1954, Interscience Publishers, New York, p. 459.

STAPHYLOCOCCI: ON THE UBIQUITOUS NATURE OF HUMAN INFECTIONS AND THEIR CONTROL BY ANTIMICROBIAL AGENTS, SINGLY OR IN COMBINATION * †

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Unlike the situation in virtually every other human infection caused by cocci, there is now no clearly described best antimicrobial therapy for penicillin-resistant staphylococcal infections. This report is concerned with in vitro studies upon staphylococcal growth as inhibited by eight antimicrobial agents, used singly and in various combinations, and with observations made in the management of 60 cases of serious staphylococcal infections in adults.

Prior to 1941 three of four patients with staphylococcal infection complicated by bacteremia died, with the course of disease mostly uninfluenced by antiserum and sulfonamides.[1, 2] From 1942 until 1946, with the use of penicillin, the mortality rate from serious infections due to *Micrococcus pyogenes* dropped appreciably.[2, 3, 4] For instance, in August, 1943, the Keefer Committee recorded the mortality rate in 91 cases of sepsis to be somewhat less than 40%.[3] By 1945 other reports indicated that less than 30% with staphylococcemia died.[1] Clinical experience in the years following 1948 revealed that mortality in cases of staphylococcal sepsis had again returned to 50% or higher.[5-8]

After 1950 we observed, as have many others, that increasing numbers of staphylococci isolated from human infections were penicillin-resistant, and infections caused by them unresponsive to treatment by it. By 1955 more than 70% of all strains recovered from patients failed to be inhibited by penicillin in vitro. Consequently, other agents were administered as therapeutic substitutes—chloramphenicol, erythromycin, tetracycline and, more recently, novobiocin and vancomycin. In 1956 we noted that the incidence of penicillin-resistant strains isolated from human infections had remained at approximately the 70% level. Contrariwise, in each year since 1952 larger numbers of isolated strains have emerged which were resistant to other antimicrobial agents, particularly tetracycline, erythromycin and novobiocin. Apparently, as these agents were administered with increasing

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frequency to patients, more resistant strains to each evolved. For example, in 1956 more than 50% of staphylococcal strains which we recovered from human infections were markedly resistant to both erythromycin and the tetracyclines.

As could be anticipated from these changes, results of single drug therapy or a variety of combinations recently described for the management of staphylococcal infections have failed to compare favorably with the therapeutic efficacy of penicillin when administered to patients with infections caused by susceptible strains. We have endeavored to remedy this therapeutic defect by studying combinations of antimicrobial agents, first in vitro, then in the patient, with the hope that a sensible prescription for clinical use could be evolved.

TABLE 1

Combination of Antimicrobial Agents Used to Inhibit Growth of *Micrococcus pyogenes*

1. Penicillin with:
   - Bacitracin
   - Chloramphenicol
   - Erythromycin
   - Novobiocin
   - Streptomycin
   - Tetracycline
   - Vancomycin
   - Chloramphenicol and Erythromycin

2. Chloramphenicol with:
   - Bacitracin
   - Erythromycin
   - Novobiocin
   - Streptomycin
   - Tetracycline
   - Vancomycin

3. Erythromycin with:
   - Bacitracin
   - Novobiocin
   - Tetracycline
   - Vancomycin

4. Novobiocin with:
   - Bacitracin
   - Vancomycin
   - Streptomycin
   - Tetracycline
   - Chloramphenicol and Vancomycin

5. Tetracycline with:
   - Bacitracin
   - Streptomycin
   - Vancomycin

METHODS OF IN VITRO STUDY

Thirteen strains of *M. pyogenes* var. *aureus,* isolated from severe human infections, were studied and their growth patterns noted after exposure to eight single antimicrobial agents—penicillin, streptomycin, bacitracin, tetracycline, chloramphenicol, erythromycin, novobiocin and vancomycin. The 13 strains were selected from over 500 recovered from patients in our laboratories since 1952. Among the group of 13, single strains showed resistance to each of the drugs except bacitracin and vancomycin, and 12 of the 13 produced penicillinase which permitted their classification as penicillin-resistant.

Twenty-four different combinations of two of the eight agents and two triple combinations were repeatedly tested (table 1). In addition, multiple

variations of concentrations of the eight drugs were examined, so that a total of more than 150 different arrangements of drugs and concentrations of drugs were assessed as to their ability to inhibit growth of staphylococci in vitro. The variations in concentrations of drug added to combinations ranged from one tenth to 10 times that amount found necessary to inhibit the strain in vitro. Organisms were tested for sensitivity to individual drugs by a modified serial dilution technic, with approximately 50,000 organisms as the inoculum. Growth curves as influenced by drugs were determined by a standard streak plate technic employing approximately 1,500,000 organisms. This method has been described for previous studies upon synergism and has proved adequate.[9]

Results In Vitro

There was a remarkable degree of reproducibility and consistency in results upon growth of the 13 strains of organisms, irrespective of the drugs used or their concentrations. The first observation of significance made upon those studied thoroughly, and confirmed by experiences with more than 500 other strains isolated from patients, was that the critical point of penicillin susceptibility was about 0.15 unit per milliliter. Organisms with a higher degree of resistance invariably produced penicillinase (by Gots' plate technic,[10]) and were, for practical clinical significance, totally resistant. We can emphasize that, in the determination of susceptibility to penicillin by either disc or tube dilution methods, the result should not be interpreted for 48 hours. On certain occasions the 24-hour reading is misleading—penicillinase production by staphylococci may be delayed for several hours and is thus not a stable event. Once initiated, however, its production cannot be neutralized by the addition of more penicillin either in vitro or in vivo.

There were variations in the degree of antistaphylococcal activity by single drugs (figure 1). Only in the instance of the penicillin-sensitive strain was there evidence of impressive control of growth, and this was accomplished solely by penicillin. In this instance, in which the strain was sensitive to 0.05 unit penicillin/ml., increasing inhibition of growth extended for 48 hours, although sterility was never accomplished.

Chloramphenicol, novobiocin and vancomycin inhibited growth to a slightly greater degree than did the others. Growth of some of the 13 strains was equally delayed by bacitracin and erythromycin; others were not interrupted to the same extent. Streptomycin and tetracycline singly interfered with growth for only a few hours and to only a slight degree. All drugs except penicillin, however, showed only transient effects, and resumption of active growth occurred by or after the twenty-fourth hour in all instances.

Similarly, only one combination of antimicrobial agents resulted in appreciable enhancement of the antistaphylococcal activity over that of a single drug. This was true regardless of initial sensitivity to or variations in

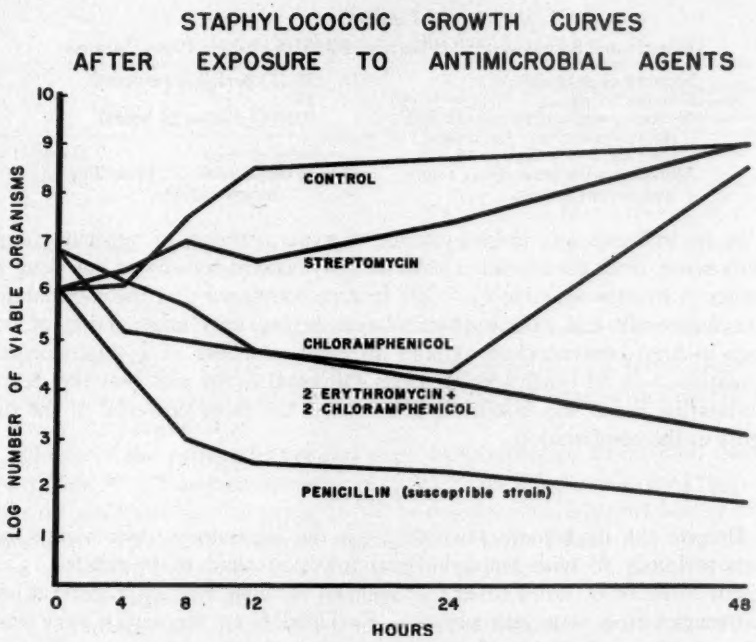

FIG. 1. Organisms used in penicillin curve sensitive to 0.05 unit penicillin/ml. All other growth patterns were upon our staphylococcus strain No. 54–767, which was sensitive to all other agents but was penicillin-resistant. 2. Growth curve as influenced by streptomycin. Pattern upon exposure to tetracycline was universally similar. 3. Growth curve as influenced by chloramphenicol essentially similar to that after novobiocin, vancomycin, erythromycin and bacitracin. 4. No other combination equaled reduction in number of organisms caused by erythromycin and chloramphenicol.

concentrations of drug added to the medium, or of inoculum size of organisms above 100,000/ml. The single effective combination was erythromycin and chloramphenicol, each added in twice the concentration of the measured sensitivity level (figure 1). This combination clearly reduced the bacterial count lower than that observed with the double concentrations of either drug alone, and growth of organism was inhibited for a longer period, i.e., for from 24 to 72 hours; at best, though, the combined effect was not strikingly bactericidal.

TABLE 2

Penicillin Resistant Staphylococci: Summary of In Vitro Observations Using Antibacterial Agents in Combination

1. Growth of staphylococci slowed for 4 to 12 hours by all agents singly and in combination
2. No one was dependably superior
3. Most marked inhibition of growth observed with double concentrations of erythromycin and chloramphenicol
4. Addition of third drug did not enhance activities of two
5. Synergism not observed with any combination

TABLE 3

Disseminated Staphylococcal Infections, All With Positive Blood Cultures

Number of patients	29 (23 penicillin resistant)
Number living	15
Mortality with erythromycin and chloramphenicol. Bacitracin used for 4 to 7 days in 10	9/19 (2 died in 24 hours)
Mortality with other drugs singly and in combination	5/10 (novobiocin, penicillin, streptomycin)

In no instance was there evidence of synergism, or of superior action in any sense, or of enhancement of antistaphylococcal activity of one drug by another or by others (table 2). We became convinced that the combination of erythromycin and chloramphenicol represented only mass action of two drugs in high concentration against different members of a staphylococcal population. In all other combinations the usual event was that the degree of inhibition noted was essentially that due to the more powerful of the two agents in the combination.

PATIENTS

Despite the inadequate rewards from the laboratory observations, patients seriously ill with staphylococcal infections had to be treated. The present series of 60 adult cases represent all of those seen on a general hospital service in a four-year period. Excluded from the series were cases with chronic staphylococcosis, such as furunculosis, with single abscesses not associated with systemic symptoms, with localized cellulitis. Children under the age of 13 were likewise excluded. Curiously, there were no cases of acute osteomyelitis in the series.

The patients uniformly were acutely ill, with fever and other clinical evidences of serious infection. The group was divided into those with positive blood cultures and evidences of disseminated infection (29 cases), and those with a large local abscess (carbuncle), or localized acute inflammation in one body system, but with negative blood culture and without evidence of metastatic lesion (31 cases) (tables 3 and 4). Generally (24 of 29) in the former group, the infection was most evident in one area, e.g., lung or heart valve, with subsequent spread from that. Among the 29 cases in the disseminated group, there were four with acute endocarditis, five with lobar pneumonia, one with generalized peritonitis, and 14 with multiple abscessed foci in lung, brain, kidney and skin (table 3). In the group with

TABLE 4

Acute Localized Staphylococcal Infections
(Abscesses 20, Primary Pneumonia 8, Pyoarthritis 3)

Number of patients	31 (24 penicillin resistant)
Number living	29
Number requiring surgical drainage	15
Number treated mainly with erythromycin and chloramphenicol	24

TABLE 5
Staphylococcal Infections

		Number of Patients	No. with Pen. Resistant Organisms	No. with Pen. Sensitive Organisms
On Hospital Admission	Disseminated	17	13	4
	Localized	13	12	1
	Total	30	25	5
Hospital Acquired	Disseminated	12	10	2
	Localized	18	12	6
	Total	30	22	8

only a single lesion (table 4) there were 20 patients with large abscesses and/or carbuncles, eight with primary pneumonia and three with pyoarthritis in one or two joints.

Thirty of the patients developed their infection prior to hospital admission (table 5). Forty-seven patients (78%) had infections caused by penicillin-resistant strains. Among the 30 with infections acquired before their entry into the hospital, five were caused by penicillin-susceptible organisms; there were eight susceptible strains among those isolated from patients whose infection was acquired after hospitalization.

Hospital-acquired infections perhaps need definition: each of the 30 occurred in a patient who was in the hospital for some medical or surgical reasons other than infection but in whom the infection first became of significance during his stay. Generally, the infection developed postoperatively or during the course of a major debilitating illness—carcinoma, heart failure, cirrhosis, bleeding peptic ulcer, poorly controlled diabetes.

The number of serious staphylococcal infections has during the last four years increased significantly, both in the group with infection started prior to hospital entry and in those acquiring the infection after admission (table 6). In the four years prior to 1957 we have treated, respectively, 28, 21,

TABLE 6
Staphylococcal Infections
Incidence

Year	Number of Patients	No. with Disseminated Infections		No. with Localized Infections	
		On Adm.	Hosp. Acquired	On Adm.	Hosp. Acquired
1953	5	1	0	3	1
1954	6	3 (1)	0	2	1 (1)
1955	21	3 (2)	4 (1)	7	7 (1)
1956	28	10 (7)	8 (3)	1	9
Totals	60	17 (10)	12 (4)	13	18 (2)

(16) Died.

six and five infections per year. The most impressive increases occurred in 1956 in the groups who entered the hospital with established infection (10 cases), and in hospital-acquired abscesses (nine cases). The mortality figures show that approximately one-half the patients with disseminated infections have succumbed (four of 10 in 1954 and 1955, 10 of 18 in 1956, and 14 of 29 over-all), whereas only two in the other group died.

As shown in table 7, 47 patients were infected with penicillin-resistant organisms. The proportion of patients with resistant infections has not changed appreciably since 1954 (four of six in 1954, 23 of 28 in 1956).

TABLE 7

Staphylococcal Infections: Penicillin Resistant Strains

	Disseminated Infection		Local Infection	
	No. with Resistant Strains	No. with Sensitive Strains	No. with Resistant Strains	No. with Sensitive Strains
1953	0	1	1	3
1954	2	1	2	1
1955	7	0	12	2
1956	14	4	9	1
Totals	23	6	24	7

CLINICAL OBSERVATIONS

Staphylococci are ubiquitous—all of us are exposed to high numbers of them constantly. Although epidemiologic studies about infections caused by them are important,[6, 7, 8] it is reasonably clear that infection can be determined by a variety of events, not necessarily related to source or to the biologic characteristics of the strain itself. There is no doubt that a number of apparently healthy people develop serious staphylococcal infections spontaneously, and that its occurrence in this setting does not diminish the over-all intensity of the infection or its outcome. In our series, for example, the worst and most fulminating infections developed in patients prior to hospital admission. Of the 29 cases of septicemia, 17 were established when the patient was hospitalized; 10 of these died.

Serious staphylococcal infections, however, are most commonly observed in patients with some chronic underlying disease process.[11] Presumably, such individuals carrying or exposed to others carrying staphylococci may develop an abscess and subsequent bacteremia as a result of some break in body defenses, initiated perhaps because of a deteriorating or spreading underlying illness, or perhaps because of trauma or a manipulative procedure. Or the opposite may obtain: a minor or latent infection may produce a worsening of the patient's underlying disease; thereafter, the infection becomes clinically more serious. Age by itself is not an important determinant

to infection—in our series of 60 cases, for instance, 23 were under 45 years of age (13 in 29 cases of sepsis). It must be emphasized also that penicillin-resistant strains are not always isolated solely from hospital-acquired infections. They are the cause of infections in persons without prior hospital experience: in our series, 25 of 30 strains isolated from patients whose infection developed prior to admission were resistant to penicillin. Conversely, not all hospital-acquired infections are caused by resistant strains —eight of 30 in our series were sensitive.

The development of a localized infection generally precedes dissemination and sepsis, but this sequence is not always clinically evident; occasionally the first lesion is small and/or transient and may be overlooked.

There is another significant feature in clinical infections caused by staphylococci which was common in both our groups of patients. The vast majority of individuals, prior to the staphylococcal infection, had been receiving one or more antimicrobial agents for a variety of indications, such as another infection, or for prophylactic reasons. Twenty-nine of the 30 patients whose infection developed while in the hospital were receiving them when the staphylococcal infection supervened, and 10 of 30 who came to the hospital with the infection already established had similarly received drugs immediately preceding the infection. Presumably, such therapy had altered their standard bacterial flora, and the change may have added to the opportunities for invasion and superinfection by staphylococci. This facet of staphylococcal infections deserves more detailed study.

Treatment of Staphylococcal Infections

In this series of 60 cases, a combination of erythromycin and chloramphenicol was used as the major regimen in 43, including six of the 13 cases caused by penicillin-susceptible strains (tables 3 and 4). Treatment of the remaining cases was extremely varied, with penicillin and streptomycin plus one or more other agents the common prescription. Summarizing the benefits derived from this program can be done simply, because results were determined mainly by the type of infection under treatment. Three are described:

1. Any staphylococcal infection caused by a penicillin-susceptible strain, i.e., less than 0.15 u/ml., should be treated with penicillin as the sole drug of choice. The dosage is determined mainly by site of infection and the ease with which penicillin can be concentrated in the lesions. Large daily doses, in excess of a million units daily at least, are recommended, and this amount should be continued for long periods. No other agent is needed in combination. Surgical drainage as adjuvant therapy in instances associated with localized pus is important. Such was required in 15 of 31 cases of localized disease, and in 13 of 29 cases of sepsis.

Mortality rates in cases of localized disease are less than 10%, and with bacteremia a mortality rate of about 33% can be anticipated.

2. Serious localized infections caused by penicillin-resistant staphylococci can be treated successfully with a combination of erythromycin and chloramphenicol, with surgical drainage as adjuvant therapy whenever indicated. The daily dose of 2 gm. of each drug has resulted in a mortality below 10% in this series—two of 31 cases died, and both had primary pneumonia. The two agents must be continued until resolution has progressed to the point of healing, usually two to three weeks, even longer in some.

If the localized disease has not produced associated serious toxicity in the host, single drug therapy is sufficient. The laboratory results of in vitro sensitivity testing is essential for the proper choice of the best drug—erythromycin, chloramphenicol and novobiocin are the ones now commonly employed.

TABLE 8

Staphylococcal Infections: Summary of Treatment Recommendations

1. There is evidence that penicillin is of value only against highly susceptible strains, i.e., those with sensitivity of less than 0.15 u/ml.

2. Combination of drugs for disseminated infections:
   a) Erythromycin plus chloramphenicol
   b) Erythromycin plus chloramphenicol plus bacitracin
   c) Vancomycin (?)

3. Single drug therapy for localized infection: Erythromycin, chloramphenicol, novobiocin, tetracycline, penicillin

4. Surgical drainage required whenever feasible

3. Antimicrobial therapy of sepsis caused by penicillin-resistant staphylococci is at the moment unsatisfactory. It is toward them almost exclusively that we have made a concerted effort to find the best drug, or a combination of them, to achieve less than a 50% mortality rate. Because of in vitro observations, the majority of our patients have received large daily doses of combined erythromycin and chloramphenicol given orally and/or parenterally. During the first few days (five to seven), bacitracin in doses ranging from 75,000 to 100,000 units daily has been added. The three-drug combination is not as effective as we had hoped. The regimen does, however, reduce mortality significantly when compared with the untreated patient, or with those treated with penicillin given in massive amounts, with or without streptomycin. In those who recover the therapy has been impressive, with remissions occurring promptly, that is, within a week, and relapses have not been observed.

In others, the regimen has cleared the blood stream of organisms, usually within 48 hours, and we have had the general opinion that the duration of the infection has been extended. This is, of course, a clinical opinion which

cannot be substantiated by clear fact. Erythromycin and chloramphenicol are administered in 2 gm. daily oral doses (less is needed if given parenterally), or between 20 and 30 mg. of each per kilogram of body weight daily.

The addition of bacitracin for a week may have added strength to the potion, although we cannot be completely certain of this. We have, however, on each occasion of its usage seen the development of kidney impairment, as evidenced by increasing cellular elements in urinary sediment after the fourth day, and eventually, on the fifth or sixth day, an elevation of blood urea nitrogen, which event precludes its further use.

Summary (Table 8)

1. This report is concerned with a description of laboratory methods designed to demonstrate the efficacy of a substitute for penicillin, and clinical experiences with the best of the substitutions so far observed. Although hardly comparable with respect to numbers of organisms killed and the speed of killing, erythromycin and chloramphenicol in combined large dosage have proved to be an effective combination to control growth of penicillin-resistant organisms. These two, with perhaps bacitracin for a few days, have proved to be as effective a combination in therapy of human infections as has been described. No other single drug or combination of them (antimicrobial therapy) has been shown to be better, consistently at any rate.

2. It has been our impression, both in vitro and in vivo, that staphylococci whose resistance to penicillin is greater than 0.15 u/ml. produce penicillinase and are, for practical purposes, penicillin-resistant. Penicillin in clinical therapy is useless in infections caused by those strains of staphylococci. Similarly, other single-drug therapy has resulted in increasing numbers of strains of staphylococci resistant to multiple other agents. In such circumstances the agent is of no clinical value either.

3. Irrespective of the importance of the epidemiologic aspects of penicillin-resistant staphylococci, it cannot be concluded that the infection hits only old persons in the hospital whose admission was necessitated by some other debilitating, noninfectious disease. Although uncommonly seen in a setting of good health, penicillin-resistant staphylococcal infections occur at all ages, in patients well removed from exposure to hospital personnel and without known experience to a contaminated source. They do, however, probably occur more often in patients receiving antibiotics for some nonspecific "prophylactic" reasons than in patients not so "protected."

4. Energetic but not unreasonably radical therapy for disseminated penicillin-resistant staphylococcal infections is indicated. A significant reduction in mortality is anticipated, although the lowering is not so great as had been hoped for. To date, no agent or combination of them is as efficacious as penicillin was in the era when the majority of isolated strains were sensitive to it. Adjuvant therapy is essential if there is localization of the infection; with pus, particularly, surgical drainage is required.

5. Although the erythromycin-chloramphenicol combination is partially effective, a better combination can be anticipated. It is hardly likely, though, that such a combination will be prefabricated into a single capsule or vial. Manipulation of dose of each most assuredly will always be needed.

6. It is our considered opinion that staphylococcal sepsis caused by strains resistant to penicillin and other antibiotics is not a hopeless infection, and that specific therapy with antimicrobials, along with proper adjuvant therapies, can be expected to result in an appreciable lowering of the present mortality rate. Inevitably a more powerful agent or agents, or a better grouping of ones now available, will be found which will interrupt rapidly and more completely the pathogenic career of penicillin-resistant staphylococci in human infections.

Summario in Interlingua

Iste reporto presenta un revista de observationes in vivo e in vitro relative a un numero de racias de staphylococcos penicillino-resistente que esseva obtenite ab infectiones human.

Un combination de chloramphenicol e erythromycina, ambes addite in grande quantitates, resultava in vitro, in le casos de omne racias testate, in un plus intense e plus permanente inhibition crescential que non importa qual altere antibiotico in administration individual o gruppo de duo o tres antibioticos in administrationes combinate.

Le resistentia a penicillina per staphylococcos es determinate exclusivemente per le capacitate del racia a producer penicillinase. In le experientia del autores, omne staphylococcos con un nivello de sensibilitate in vitro de plus que 0,15 unitates de penicillina pro millilitro es productores de penicillinase e require esser considerate, ab le puncto de vista de practic objectivos clinic, como penicillino-resistente. Nulle quantitate de penicillina addite al medio continente organismos de iste genere es unquam capace a restringer le inevitabilitate de lor plen crescentia.

In le tractamento de humanos, le sequente recommendationes es presentate pro le therapia de infectiones per staphylococcos de typo penicillino-resistente:

1. Pro infectiones localisate—abscessos, per exemplo—un sol antibiotico es adequate, providite que un bon grado de drainage es obtenite. Erythromycina e chloramphenicol es le drogas de election in iste caso.

2. Pro serie e disseminate infectiones staphylococcal, le administration diurne de 2 g de chloramphenicol e de erythromycina es proponite. Le addition de 100.000 unitates diurne de bacitracina durante quatro a septe dies e le drainage chirurgic de lesiones que es accessibile es mesuras adjuvante. Con iste regime, le mortalitate in consequantia de sepsis staphylococcal deberea esser levemente infra 50 pro cento.

In le caso de organismos que es exquisitemente susceptibile al effecto de penicillina, le sol tractamento de election es penicillina, e un secunde droga non es requirite, sin reguardo al typo de infection.

Le autores conclude que iste regimes es non ancora satisfactori sed que al tempore presente illos es le meliores disponibile.

BIBLIOGRAPHY

1. Anderson, D. G.: Treatment of infections with penicillin, New England J. Med. **232**: 400–405 (Apr. 5) 1945.
2. Mitchell, O. W. H., and Chapman, O. D.: *Staphylococcus aureus* septicemia, New York State J. Med. **40**: 1308–1311 (Sept.) 1940.

3. Penicillin in treatment of infections: a report of 500 cases. Statement by the Committee on Chemotherapeutics and other Agents, C. Keefer, Chairman, Division of Medical Sciences, National Research Council, J. A. M. A. **122**: 1217–1224 (Aug. 28) 1943.
4. Dowling, H. F., Lepper, M. H., Caldwell, E. R., and Spies, H. W.: Staphylococcic endocarditis: an analysis of 25 cases treated with antibiotics, together with a review of recent literature, Medicine **31**: 155–176 (May) 1952.
5. Hansmann, W., and Karlish, A. J.: Staphylococcal pneumonia, Brit. M. J. **2**: 845–847 (Oct. 13) 1956.
6. Knight, V., and Collins, H. S.: Current view in the problem of drug resistant staphylococci and staphylococcal infections, Bull. New York Acad. Med. **31**: 549–568 (Aug.) 1955.
7. Rogers, D. E.: The current problems of staphylococcal infections, Ann. Int. Med. **45**: 748–781 (Nov.) 1956.
8. Wise, R. I., Cranny, C., and Spink, W. W.: Epidemiological studies on antibiotic resistant strains of *Micrococcus pyogenes*, Am. J. Med. **20**: 176–184 (Feb.) 1956.
9. Bunn, P., Canarili, L., and Osborne, W.: Activity of certain combinations of antimicrobial agents upon *Pseudomonas aeruginosa*. Antibiotics Annual 1953–54, pp. 279–284, Medical Encyclopedia, Inc., Publishers, N. Y. C.
10. Gots, J. S.: Production of extracellular penicillin-inactivating substances associated with penicillin resistance in *Staphylococcus aureus*, Proc. Soc. Exper. Biol. and Med. **60**: 165–168 (Oct.) 1945.
11. Osler, W.: Practice of medicine, 7th Ed., 1909, D. Appleton & Co., New York, p. 215.

PSYCHOLOGIC FACTORS IN CHRONIC ALCOHOLISM *

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Statement of Problem

The decision of The American College of Physicians to hold this symposium on the problem of alcoholism, and to bring the combined viewpoints of internist, sociologist and psychiatrist to bear on it, reflects our modern medical recognition of chronic alcoholism as a disease of major medical importance. This in itself marks a significant step in our understanding of this disorder, for it signifies the surmounting of the moral frame of reference within which chronic alcoholism has so long been regarded as a manifestation of ignorance, of vice, of sinfulness, or of all of these combined.

In advancing thus from a moral to a medical frame of reference—that is, in studying chronic alcoholism as a disease (which, incidentally, severely disables some 4,000,000 American citizens)—we have also, I think, come to common agreement that, by and large, the roots of what makes an individual drink are to be sought in the psychologic structure of that individual and in his interaction with the social milieu within which he moves. Though we all recognize the interesting researches of such workers as Williams, who postulates inborn errors of vitamin metabolism in alcoholic patients, I think again that the presence of this panel, constituted in this particular way, indicates how widespread is our conviction of the major determinant role of psychologic and social factors in the genesis of the alcoholic disorder.

This conviction has been built up through a long period of study under the aegis of modern dynamic psychiatric theory, a period devoted to the seeking of those common psychologic denominators which could be said to characterize the alcoholic patient. Knight's classic paper, "The Dynamics and Treatment of Chronic Alcohol Addiction" is just such a systemic statement, within a psychoanalytic frame of reference, of the major psychologic themes found in a group of 30 alcoholic patients treated with intensive psychotherapy. The increased knowledge of the nature and dynamics of the alcoholic process and of the character structure of the alcoholic patient that emerged from such psychotherapeutic investigations has not, however, been significantly translated into increased therapeutic effectiveness. The gap

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between what seemed to be valid psychologic understanding and the effectiveness of our treatment methods has been an uncomfortably wide one. Though Knight carefully analyzed the dynamics operative in his patients, he refrained from a quantitative assessment of extent and duration of "cure." Nor is opinion essentially different in the broader context of general psychiatric interest in this disorder. Despite a seemingly ample body of theoretic-scientific understanding, psychotherapists working with a large variety of technics, including face-to-face psychotherapy, group therapy, and even hypnotherapy, have met with a parallel lack of sustained success.

Certainly this state of affairs is no secret, and is reflected in the frustration the internist so often feels with the limited effectiveness of psychiatric therapeutic efforts to date. The question, What is the appropriate treatment method for the alcoholic? has no effective answer in these terms, and the wide variety of psychologic, physiologic and pharmacologic therapeutic modalities proposed in the literature constitutes a confusing web of contradictory and canceling claims and evidence.

It may, however, be possible to break through this seeming impasse if we shift from an over-all psychologic frame of reference, devoted to isolating the common denominators characteristic of the alcoholic in general, to a particulate psychologic frame of reference, devoted to a study of the pattern and range of individual differences among alcoholic patients. That is, the question, What is the appropriate treatment method for the alcoholic? can be translated into the question, Which treatment method of those available is appropriate to which kind of alcoholic patient—and why? Within this framework, alcoholism is seen as a broad umbrella which covers many common psychologic factors, but also a broad spectrum of psychologic differences, and it can be hypothesized that different treatment approaches could be differentially helpful to different kinds of alcoholic patients.

The research project that I wish to report on to this group is devoted to the exploration of this hypothesis—that varying treatment methods can be differentially prescribed to different kinds of alcoholics and, as such, is an example of the kind of particulate psychiatric approach that I think stands on the current frontier of psychologic understanding of this disorder.

Organization of the Project

This project comprised 178 patients at Winter Veterans Administration Hospital studied through two and a half years of treatment and two years of follow-up. It arose out of our discouragement with the kind of treatment program in existence on our wards prior to its onset, which had been built around the familiar model of individual and group psychotherapy, an active milieu program, and coöperation with Alcoholics Anonymous for selected patients.

The decision was crystallized to create a frankly experimental treatment unit. A number of treatment modalities, which had drawn insistent atten-

tion by virtue of greater claimed empiric success and/or presumed valid underlying psychologic theory, were selected for comparative evaluation within a time-limited mental hospital setting. The three specific treatment modalities chosen were Antabuse, conditioned-reflex, and group hypnotherapy—to be offered side by side on the same ward; a fourth group was to serve as the control group. (We called this fourth group the "milieu therapy" group, because it was felt that a specific psychologic handicap would be posed for patients who felt themselves to be only members of a "control group.")

We were interested first in the question, Is any treatment for the hospitalized alcoholic patient more effective than another? Using a multidimensional measure of improvement, in which degree of abstinence was considered to be but one of a variety of relevant indices, we hoped to determine whether any of the offered treatment programs should be the treatment of choice for the hospitalized patient, or if none merited such preferential usage in their present state of development.

In keeping with the view which regards alcoholism as a symptomatic expression of deep-seated emotional difficulty, we separated alcoholic patients into different psychiatric nosologic categories in terms of their basic psychologic differences. Thus with *random* application to a representative alcoholic population covering the whole array of psychiatric syndromes—the psychotic, the character disorder and the neurotic—an opportunity would exist to assess the efficacy of each modality in terms of which kinds of alcoholic patients it helped. In this way, our second major set of hypotheses, built on the differential indications for our selected modalities, could emerge.

As far as possible, the ward was set up to be much as it had been in the days prior to the project, which, for the control group, would comprise the totality of their treatment program. Distinguishing differences between groups were created by the specific modalities superimposed. Antabuse patients had their dosage regulated through a series of carefully studied Antabuse-alcohol trials. An authoritative, firm attitude was maintained in regard to the taking and continuance of the drug, despite minor troublesome side reactions. The conditioned-reflex patients were each given a five-day course of conditioning, followed (on the sixth day) by a trial of liquor without the unconditioned stimulus. For each patient the conditioning was reinforced before hospital discharge and again at each follow-up visit. With the hypnotherapy patients, induction was carried on in the group, supplemented by individual induction where this was additionally helpful.

Results

Over-all results for the four treatment modalities in terms of the gross categories—improved, unimproved, and lost to follow-up—indicate that more patients did well with Antabuse (53% improved) than with any other

proffered modality. (Improvement rates with the others ranged from 24 to 36%.) In terms of this first statistic, Antabuse conformed to its claimed effectiveness in helping alcoholics to greater sobriety and more improved adjustments.

Within each modality we still, however, faced the problem of ascertaining those kinds of alcoholic patients likely to be helped by its application—and why. Our approach to this differential study has been in the assessment of the psychologic meanings of the modality and the kinds of patients who are best able, in terms of their particular psychologic make-ups, to fit into these psychic demands. That is, we postulated that each treatment method carries with it a distinct and different psychologic impact, and further, that the patient's response is determined in large part by the interaction of these specific psychologic meanings of the modality with the psychologic need-systems of the individual patient.

1. *Antabuse:* For instance, with Antabuse we were interested in the psychologic meanings attached to the drug and its mode of administration that could throw light on the question of which kinds of alcoholic patients would be likely to continue to take it. Antabuse is a drug, given by mouth, with potent physiologic effects. Psychologically, this is the replacement of a harmful object (alcohol) by a good object (Antabuse), the exchange being made under the guidance of a benevolent external authority, the doctor. Another distinct aspect of the Antabuse experience is in the almost complete certitude of enforced abstinence while on the drug. That is, with Antabuse it is an external agent that controls the impulse to drink, and the maintenance of this longed-for sobriety is made relatively certain. As expected, therefore, the Antabuse patients were the most satisfied and compliant treatment group. Since nothing more was demanded of them than the regular taking of a pill, which was easy in the hospital, these patients experienced little inner psychic disequilibrium. Once they were outside the hospital, and confronted anew with the problems of life to be met now without recourse to alcohol, anxiety again erupted, and what was called by many patients "the battle of will power" began.

We found that in maintaining a sober state out of the hospital, the more compulsive the psychologic make-up of the patient, and the more he could build compulsive routines and ceremony around the taking of Antabuse, the better his prognosis. Any number of patients stated that the urge to abandon Antabuse and return to drink could be dispelled only by keeping busy, by compulsive and constraining routines. Antabuse lent itself well to this need for unvarying routines. The pill each day at a particular time gave the patient a concrete task of paramount symbolic importance. And the more compulsive the individual was in every aspect of his personality functioning, the more likely his improvement with Antabuse. Many patients were able to erect newfound compulsive routines around their dependent ties to the hospital and to the physician, to whom they returned

periodically. For instance, of nine markedly improved patients followed for a full two years, six signaled the end of their formal contact with the project by heavy bouts of drinking—for each, the first "binge" in the two years. This suggests that the effective use of Antabuse may well be linked to the necessity to offer it through a continuing relationship of indefinite duration.

Implicit in our conception of the meaning of Antabuse are the contra-indications which emerged. For some patients the certainty of enforced sobriety can be psychologically disastrous. In our experience this seemed to hold for two groups, the borderline schizophrenic, and those warding off deep depressive reactions, in both of which groups the drinking itself helped stave off a more serious schizophrenic or depressive decompensation. Among a total of five patients in the borderline schizophrenic group, only one improved. One was driven to a florid psychotic state which began to erupt even before the drug was started, and which did not remit when the patient was shifted onto placebos. The other three patients in this group early fled the hospital and reverted to drinking, being among the small number of the total Antabuse group who failed to complete the treatment course. The one chronic depressed patient among those on Antabuse became even more depressed as he left the hospital in a sober state. Of two patients with manic-depressive personality tendencies, one went into a manic psychotic flight when the day for the starting of his Antabuse approached. The third psychotic reaction occurred in an individual with a mild organic brain damage. In this patient the reaction seemed to be a toxic-organic psychosis related directly to drug dosage, unlike the other two described, which emerged under the impact of the threatened administration of the drug.

2. *Conditioned-Reflex:* Conditioned-reflex therapy can be understood psychologically as representing a drastic agent directed from the outside which the individual is powerless to control. In this way, it is the most threatening of the therapies and, accordingly, we can look for the relevant personality dimensions among the variables of the individual's characteristic responses to aggression and his psychologic reactions to punishment.

As it worked out, the assessment of the strength of the aggressive components in the psychologic make-up of the patients was a significant index of the response to this treatment. When measured along a continuum in terms of the strengths of the aggressive character components, the more aggressive patients did significantly less well by every criterion measured. As a group they had the highest degree of failures to complete the treatment, almost none of them maintained regular follow-up contact, and they had the poorest over-all improvement rates.

Contrariwise, a group who, it was felt, might respond favorably to the conditioned-reflex method was the clinically depressed. It was felt that the perceived punishing aspects of the treatment modality might help alleviate

the intense guilt of the depressed patient, and we found that among those on conditioned-reflex therapy, the clinically depressed patient improved markedly.

In general, improvement was most marked where the conditioning experience was perceived as a partial rather than a complete barrier against drinking. Unlike Antabuse, where a large measure of its effectiveness lay in the possibility of minimal involvement on the part of the patient, conditioned reflex, being so psychologically threatening a therapy, was most successful where active involvement and coöperation were obtained by presenting it as a partial barrier requiring constant support by the patient. The more it was represented as an absolute barrier, the more the patients felt impelled to test it; the more "aggressive" their character make-up, the more likely they were to do so.

3. *Group Hypnotherapy:* The group hypnotherapy modality was conceptualized as one that provided the patient with an experience of psychologic surrender and loss of control. It was felt that this might evoke positive response in passive, shy individuals who find it difficult to establish relationships despite their strong wish to do so. Hypnotherapy might make it possible to reach such individuals and permit a psychic surrender in an atmosphere which would pose a minimal threat to their psychic organization. Conversely, the greater the tendency to discharge tension actively and aggressively, the poorer the response might be to this modality.

In keeping with our expectations, based on certain theoretic assumptions, the alcoholic patients were quite hypnotizable. When hypnotizability was assessed against diagnostic groupings, the striking finding was in the potentiality for deeper hypnosis of the individuals in the passive and dependent character groups.

In the assessment of diagnostic categories against ultimate treatment results, the patients in the passive and dependent group did the best. As a group, these patients were the most hypnotizable, maintained a good record of treatment completion, showed the best over-all improvement record, and were the most regular in follow-up contact.

In contradistinction at almost every point to the passive and dependent character group was the behavior in hypnotherapy of the more aggressive group. These patients showed the poorest hypnotizability and the greatest number of failures to complete treatment and to return for follow-up visits. These patients had developed aggressive and strongly manipulative behavior as barriers against their own dependency longings. Hypnotherapy posed a specific threat to these life-long protective operations.

The schizoid and schizophrenic category was a group that showed a high degree of treatment completion (seven out of 10) but the very smallest improvement rate of all groups in hypnotherapy (only one out of the 10). These psychotic patients seemed able to accept being hypnotized and the identification with the therapist as long as they were within the security of

the concrete treatment structure. But these ties seemed too tenuous to maintain from outside the hospital.

4. *Milieu Treatment:* The fourth group, milieu treatment, was originally set up as a control group. Many patients experienced placement in this group with considerable disappointment and resentment because it did not carry a "glamorous" and externally directed therapeutic device.

It soon became evident, however, that specific psychologic meanings attached to placement in this group, and that the milieu treatment could not be conceptualized simply as a control for the other modalities. The common complaint—that they had none of the promising extra modalities—served to unify the group members, and this, coupled with the consistent availability of both individual and group psychotherapeutic help, seemed to crystallize the acceptance of psychotherapy as the differentiating and specific organizing focus of this group. At their request, the milieu treatment patients were seen twice weekly for group psychotherapy, as against once with the other three groups.

In keeping with this evolution of the milieu treatment group into more than a control group, specific indications for this modality emerged. It is that treatment group in which the patients must assume the major responsibility for their own change by virtue of the fact that they have the fewest external devices upon which to hang their problems and responsibilities. It became, therefore, the treatment group closest to individual psychotherapy. Those who could make the best use of it were those who represented the best psychotherapy prospects. In addition, for those patients for whom the other modalities with their special attributes are specifically contraindicated, the milieu treatment program represents the preferential avenue of approach. We have in mind especially patients who cannot tolerate an abrupt transition to an enforced sobriety without the threat of severe psychologic disorganization.

In this modality, improvement seemed to correlate directly with the strength of the patient's attachment to doctor, hospital, and treatment program. The ability of the patient to form stable, predominantly positive attachments, of course, figures prominently in prognostic assessments in each of the modalities. Its significance is heightened, however, with the patients of the milieu treatment group consequent to the absence of any differentiating and externally imposed "extra" modality.

Discussion

These first results from our Alcoholism Research Project—covering two and a half years of treatment, two years of follow-up, and 178 patients—are presented not because of the precision of the conclusions, but rather as an example of a particularized psychiatric research approach geared to the simultaneous pursuit of two main kinds of questions. In answer to the first question, Is any treatment for the hospitalized alcoholic patient more effective

than another? we have seen that Antabuse emerged as more helpful to more patients than any of the other offered modalities. Yet the group not helped with Antabuse was sufficiently large (almost half), and the group helped with each of the other specific modalities also sizable enough, that the problem of the optimal mental hospital management of the alcoholic patient could not be resolved into a blanket prescription of management with Antabuse. Rather, our second question had to be pursued, namely, the differential indications for the various modalities based on the differences in the psychologic make-ups of our patients and the consequent differences in the kind of therapeutic approach that would best meet their particular personality needs.

It is this search for differential treatment indications, rationally based on our understanding of the psychologic meaning and impact of the treatment, and the kind of patient psychologically best constituted to respond to it, that we feel represents our particular approach and contribution to this complex problem. The statements we have made here represent but a first step in this desired direction. The next step would be in the design of a successor project, set up exactly as was this first, with the exception that patients would be assigned to a treatment modality not randomly, but specifically in accord with the tentative criteria arrived at in this study. If our criteria are fruitful, an increase in the treatment success in each modality should ensue, and, of course, out of such a successor study guides would emerge for the refinement and revision of these first hypotheses.

Before closing, I would like to mention some of the limitations of a project such as this. This study covered not the whole cross-sectional alcoholic population, but just those patients admitted to a closed ward of Veterans Administration hospital and under certain specific stipulations. Furthermore, only a portion of the available therapeutic spectrum was offered. This project specifically limited itself not only to four treatment plans, but also to the use of each in an unvarying and specifically limited way. For instance, one suggested formulation from the results with Antabuse is that, as applied in this project with these particular patients, it helped organize the patients in such a way that they felt lesser rather than greater need for individual psychotherapy. The conclusion might be extrapolated that the use of Antabuse poses a specific barrier to the engagement of the patient in psychotherapy. Such a conclusion would be unwarranted as a generalization beyond this particular setting—a closed ward in a mental hospital. Study of a different kind would be necessary to show the various ways in which Antabuse could be used helpfully in conjunction with individual psychotherapy, as well as destructively as a weapon against it. Various *combinations* of therapies might thus be helpful in individualized ways that could not readily emerge in our particular project design. On this question, our own project can point only to the need for intensive, longitudinal studies yielding data that will shed complemental light on the treatment enigma that chronic alcoholism still poses.

SUMMARIO IN INTERLINGUA

Le investigation psychiatric del processo designate como alcoholismo se ha concentrate depost longe tempore super le discoperta de commun denominatores psychologic de que on poterea dicer que illos characterisa le patientes alcoholic. Le programma de recercas hic reportate es un exemplo del typo *particularisate* de methodologia psychologic, adaptate a un studio del character e del grado de differentias individual inter le patientes de alcoholismo. Isto significa que le question "Que es le appropriate methodo therapeutic pro alcoholicos?" es reimplaciate per le question "Qual methodo ab inter le methodos disponibile es appropriate pro qual typo de patiente de alcoholismo—e pro qual ration?"

Quatro formas de therapia—Antabuse, reflexo conditionate, hypnotherapia de gruppo, e tractamento per milieu—esseva applicate al hasardo a un representative population de alcoholicos, includente casos de omne le varie syndromes psychiatric, con le objectivo de determinar le efficacitate del formas individual de therapia con respecto al question de qual forma esseva de adjuta a qual typo de alcoholico. Super le base del datos colligite in le curso del studio, criterios esseva disveloppate pro le prescription differential del quatro formas de therapia pro differente typos de alcoholico, i.e. typos con differente organisationes characterologic. Cata un del methodos therapeutic se distingueva per un specific e differente impacto psychologic, e le responsas del patientes individual esseva determinate in grande mesura per le interaction del specific signification psychologic del therapia usate con le systema de requisitos psychologic in le patiente mesme.

THE CLINICAL PATTERNS OF SMALL-BOWEL TUMORS: A STUDY OF 32 CASES *

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Few articles in the literature [1-4] have been concerned primarily with the early clinical patterns of small bowel tumors. We reviewed the records of a relatively large number of patients who had small bowel tumors and found that the correct diagnosis was rarely made or suspected at the time of the initial examination. We appraised the symptoms, signs and laboratory findings of these patients to determine the indications for and the accuracy of roentgen studies, as well as the indications for diagnostic celiotomy.

Table 1

Locations and Pathologic Diagnoses of 32 Cases of Small-Bowel Tumor

	Malignant			Benign	Total
	Adenocarcinoma	Carcinoid	Lymphosarcoma or Sarcoma		
Duodenum	2	0	0	1	3
Jejunum	14	1	2	4	20
Ileum	1	1	6	0	9
					32

Material

The patients in this study were examined in the Pratt Diagnostic Clinic or the New England Center Hospital and proved to have, at operation or necropsy, a primary tumor of the small bowel, which had clearly caused symptoms or signs. Cases were excluded where the tumor was an incidental finding at operation or necropsy, or where the primary site was the ampulla of Vater or organs other than the small bowel.

Table 1 lists the location and histologic diagnosis of the tumor in the 32 cases in this study. It is evident that adenocarcinomas are more common in the upper part of the small intestine, whereas sarcomas are more common in the ileum. Three of the five tumors listed as lymphosarcoma

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TABLE 2

Clinical Pattern in 32 Cases of Small-Bowel Tumor

Case	Sex	Age	Diagnosis	Clinical Pattern	History					P.E.	Laboratory		Diagnosis Made by
					Nausea and Vomiting	Crampy Abdominal Pain	Other Pain	Weakness and Fatigue	Melena	Mass	Anemia*	Stool Guaiac	
1	M	74	Adenocarcinoma duodenum	Obstruction	+	0	+	+	+	0	+	+	X-ray
2	M	57	Adenocarcinoma duodenum	Obstruction	+	0	+	0	0	+	+	+	X-ray
3	M	35	Adenocarcinoma jejunum	Blood loss	+	+	0	+	0	0	+	+	X-ray
4	F	65	Adenocarcinoma jejunum	Blood loss	0	0	0	+	0	0	+	0	X-ray
5	F	40	Adenocarcinoma jejunum	Obstruction	+	+	0	0	0	0	0	0	X-ray
6	F	49	Adenocarcinoma jejunum	Blood loss	+	+	+	+	0	0	+	+	X-ray
7	M	57	Adenocarcinoma jejunum	Obstruction	+	0	0	+	0	0	0	0	Necropsy†
8	M	48	Adenocarcinoma jejunum	Blood loss	0	0	+	+	+	+	+	+	X-ray
9	F	49	Adenocarcinoma jejunum	Pain	+	+	+	+	0	+	0	+	X-ray
10	M	41	Adenocarcinoma jejunum	Obstruction	0	+	0	0	0	0	0	0	Operation
11	M	71	Adenocarcinoma jejunum	Blood loss	+	+	0	+	+	0	+	+	Operation
12	M	21	Adenocarcinoma jejunum	Obstruction	+	+	0	0	0	0	+	Not done	Operation‡
13	F	32	Adenocarcinoma jejunum	Obstruction	+	+	0	+	0	0	+	+	X-ray
14	M	51	Adenocarcinoma jejunum	Obstruction	+	0	+	Unknown	Unknown	0	Unknown	Not done	X-ray
15	F	55	Adenocarcinoma jejunum	Obstruction	0	+	0	+	0	+	+	+	X-ray

* Hemoglobin below 9.0 gm./100 ml. in females and 11.0 gm./100 ml. in males.
† The only roentgen study was a plain abdominal film.
‡ No roentgen studies.

TABLE 2—*Continued*

Case	Sex	Age	Diagnosis	Clinical Pattern	History					P.E.	Laboratory		Diagnosis Made by
					Nausea and Vomiting	Crampy Abdominal Pain	Other Pain	Weakness and Fatigue	Melena	Mass	Anemia*	Stool Guaiac	
16	M	45	Adenocarcinoma jejunum	Fever	0	0	0	+	0	0	+	+	Necropsy
17	M	55	Adenocarcinoma ileum	Blood loss	0	0	+	+	0	0	+	+	Necropsy
18	M	49	Carcinoid jejunum	Obstruction	0	+	0	0	0	0	0	0	X-ray
19	M	47	Carcinoid ileum	Flushing	0	0	0	0	+	+	0	+	X-ray
20	F	43	Lymphosarcoma jejunum	Obstruction	+	+	0	−	0	+	0	+	X-ray
21	F	30	Lymphosarcoma jejunum	Fever	0	0	+	+	0	0	0	0	Operation‡
22	M	39	Lymphoma ileum	Pain	+	+	+	+	+	0	0	+	X-ray
23	M	35	Lymphosarcoma ileum	Pain	0	+	+	+	0	0	+	0	Operation
24	M	60	Lymphosarcoma ileum	Obstruction	0	+	0	+	0	0	0	Not done	X-ray
25	M	24	Lymphosarcoma ileum	Obstruction	+	+	+	0	0	+	0	−	X-ray
26	M	34	Leiomyosarcoma ileum	Blood loss	0	0	0	+	+	0	+	0	Operation
27	F	49	Fibrosarcoma ileum	Blood loss	0	0	0	+	+	0	0	0	Operation
28	F	48	Lipoma jejunum	Blood loss	0	+	+	+	+	0	+	+	X-ray
29	M	56	Neurofibroma jejunum	Blood loss	0	0	0	+	+	0	+	+	X-ray
30	F	66	Hemangiopericytoma jejunum	Blood loss	0	0	0	+	+	0	+	+	Operation
31	F	17	Adenoma jejunum	Blood loss	0	0	0	+	0	0	+	+	Operation
32	F	51	Adenoma duodenum	Blood loss	0	0	+	+	0	0	+	+	X-ray

were classified by the pathologist as reticulum cell sarcomas, another as malignant lymphoma, and the fifth simply as lymphosarcoma.

Table 2 lists the cases and their important diagnostic features. Four patients had unusual features in association with their small bowel tumors. The syndrome of intestinal polyposis and melanin spots of the oral mucosa, lips and digits was present in case 12 (adenocarcinoma of the jejunum).[5] One large polyp which histologically was a polypoid adenocarcinoma caused an intussusception which required emergency operation and resection. In case 19 the patient had only postprandial flushing of the face and hands. This led to the finding by roentgen study of the carcinoid of the ileum. In cases 26 and 27 the tumors were histologically sarcomas, though they were of a very low grade of malignancy.

Clinical Pattern

Although all patients had a number of the symptoms and signs listed in table 2, a predominant clinical pattern was evident in each case and this is the basis for the following classification.

Most patients had one of two clinical patterns. The first, which we have labeled *obstruction,* occurred in 14 of the cases and was characterized by a history of recurrent attacks of crampy, midabdominal pain, often with nausea and vomiting. These patients often did not have complete occlusion of the bowel lumen, but did have intermittent excessive peristalsis as a result of partial stenosis or rigidity of a segment of the bowel. Nausea and vomiting with very little pain were the manifestations of obstruction in the two patients with duodenal tumors.

The other prominent clinical pattern, which occurred in 12 of the cases, was that of *blood loss.* These patients usually complained of weakness and were often known to have been anemic. Seven of the 12 patients in this category had melena. Four patients (cases 26, 27, 30 and 31), all of whom had relatively benign tumors, gave histories of intermittent severe bleeding with sudden weakness, melena and anemia. The five patients in this group who had malignant neoplasms seemed to have steady and less severe bleeding. Some gave no history of melena, although they were severely anemic and had occult blood in their stools.

The remainder of the patients had a variety of other clinical patterns. Three (cases 9, 22 and 23) had constant abdominal or thoracic pain unlike the crampy pain in the obstruction group. Fever was the predominant symptom in two cases. Case 21 (lymphosarcoma of the jejunum),[6] a 30 year old woman, had persistent severe fever during a three-month hospitalization. There were never any significant gastrointestinal symptoms. Perforation of the jejunum at the site of the tumor led to operation and, later, necropsy. Similar cases are reported by Irvine and Johnstone.[7] In case 16 (adenocarcinoma of the jejunum) fever was the most prominent feature

of the patient's 19-month illness. There were no gastrointestinal symptoms, and the diagnosis was finally made by necropsy.

The individual symptoms in all cases were reviewed. The important symptoms are listed in table 2. In addition, weight loss of over 10 pounds occurred in all but six of the 27 patients with malignant tumors, and in none of the five with benign tumors.

Abnormalities in the physical examination were few except for the patients seen during acute small-bowel obstruction. Evidence of poor nutrition or of pallor correlated with the history of weight loss or the finding of anemia. The observation of flushing of the skin or unusual pigmentation has already been mentioned. An abdominal mass was felt in only seven of the 32 patients. Enlarged peripheral lymph nodes were not found in any patient, and the spleen was palpable in only one (case 23).

The results of laboratory tests in all of the cases were surveyed, but the only common abnormalities were anemia and occult blood in the stools. A few patients did have a lowered serum albumin associated with poor nutrition. Significant anemia (hemoglobin below 9.0 gm./100 ml. in females, and 11.0 gm./100 ml. in males) occurred in 19 of the 31 cases for whom the figures were available. The hematologic indices and blood smear usually showed evidence of hypochromic anemia. Occult blood was found in the stools of 19 patients.

In summary, there were two main clinical patterns in these patients—obstruction and blood loss. Recurrent, crampy abdominal pain was the main symptom of the obstruction group. In the blood loss group, intermittent severe bleeding often occurred with the benign tumors. Constant occult blood loss was commonly found in the patients with malignant tumors. It is important to note that, although these patterns are characteristic of small-bowel tumors, they may also be produced by tumors elsewhere in the gastrointestinal tract. For instance, a duodenal or high jejunal tumor may cause the same symptoms as an adenocarcinoma of the stomach, whereas a tumor in the distal part of the ileum may produce the same symptoms as a cecal adenocarcinoma. When a patient has one of these clinical patterns it is wise to request that the radiologist first perform an ordinary examination of the stomach and duodenum or colon. If this does not show an abnormality which explains the symptoms, it is important to request special small-bowel roentgen studies.

Roentgen Studies

Tumors of the small intestine may present roentgen abnormalities demonstrable by plain film or contrast studies. In 30 of the 32 cases, plain films were available for review. Multiple dilated intestinal loops indicated small bowel obstruction in two of these (cases 5 and 25). In three others (cases 18, 19 and 24) one or two of several plain films showed some slightly dilated, gas-filled small-bowel loops. This finding was not helpful. A

dilated stomach was seen in two patients with jejunal lesions (cases 7 and 14). In one of these (case 14) the observation of a dilated stomach filled with gall-bladder dye led to the demonstration of a jejunal adenocarcinoma. In the other (case 7) the patient died before other studies could be done. We had no case in our series in which there was an abnormal soft-tissue mass with a gas shadow outlining an ulcerated tumor cavity.[8]

Contrast studies with barium solutions were done on 29 patients of this series. Suspected small-bowel obstruction does not contraindicate this kind of study. In 11 cases a routine gastrointestinal series consisting of fluoroscopy, films of the stomach and duodenum, and a follow-up film, usually taken 90 minutes later, demonstrated the tumor. Three were located in the duodenum (cases 1, 2 and 32). Duodenal tumors represent a diagnostic problem different from that of lesions in the remainder of the small intestine, since the examination of the duodenal loop is usually part of the routine stomach examination. In three additional patients (cases 4, 9 and 14) the tumor was located high in the jejunum and was seen on a film of the stomach and duodenum. In five other instances (cases 6, 8, 13, 15 and 29) the lesion was identified on a follow-up film taken at 90 minutes, and confirmed by reëxamination with fluoroscopy and spot films. In the lesions which were difficult to find, the observation of a hoop-shaped loop just proximal to the tumor was helpful.

Five of the tumors (cases 3, 18, 20, 24 and 28) were discovered with a complete small-bowel roentgen examination consisting of frequent fluoroscopic and radiographic observations after oral ingestion of barium solution. Additional technics, such as small-bowel enema or injection of barium through an intestinal tube at the site of obstruction, were used only occasionally to confirm the presence of tumors seen by simpler methods.

Two low ileal lesions (cases 19 and 22) were seen and a third one was suspected (case 24) in the course of a barium enema examination.

The roentgen patterns of small-bowel tumors are characteristic and are easily recognized by the experienced observer. The discovery of 11 tumors during routine upper gastrointestinal roentgen study illustrates this point. The alterations resemble those produced by tumors in the colon: polypous masses (case 22) a nodular ulcerated pattern with narrowing of the lumen (case 6, figure 3), widening of the lumen if the tumor develops extraluminally and tends to be necrotic (case 15), or annular constricting deformities (case 14).[9, 10] Single lesions of lymphosarcoma may be indistinguishable from adenocarcinoma. However, lymphosarcoma may also cause a picture of dilated but rigid segments of bowel in which giant rugae are seen. Benign lesions may present a soft, polypous, intraluminal mass or broad-based filling defects. Intussusception may occur with malignant or benign tumors.[1, 11] Intramural tumors, which have grown away from the lumen, often do not produce any roentgen abnormalities (cases 26, 27 and 30).

We thought it of interest to consider in detail the cases where the diagnosis was not made by roentgen studies. There were 27 patients with malignant tumors in our series. Two had no roentgen studies, and one had only plain films. The lesion was seen in 15 of the 24 patients examined with contrast studies, and suspected because of obstruction in two others. In seven, therefore, the diagnosis was missed (cases 10, 11, 16, 17, 23, 26 and 27). In three of these (cases 10, 11 and 23) no small intestinal studies were done, and a single follow-up film in the course of a routine gastrointestinal examination did not show the affected small-bowel segment. Examination of the small intestine would probably have resulted in the demonstration of the lesion. In the fourth patient (case 17) the lesion was overlooked but could be seen when the films were reviewed. In the fifth case the films were not available for review but the examination was reported to show no abnormality. In the last two cases the tumor did not project into the lumen. This kind of tumor probably cannot be visualized by roentgen studies.

Five patients who had benign tumors were examined by contrast study, and in two the lesion was not seen (cases 30 and 31). One of these was an extraluminal tumor. The other (case 31), who had a small adenoma of the jejunum, was not subjected to repeated studies, since operation was indicated because of severe blood loss.

Depending upon the criteria used, the diagnostic accuracy of roentgen studies of small bowel tumors reported in the literature varies markedly.[12, 13, 14, 15, 16] In our patients who had contrast studies, the tumor was visualized in 18 and the diagnosis of small-bowel obstruction was made in an additional two. Of the cases where the diagnosis was missed by roentgen examination, three could not have been diagnosed because of their extraluminal location, three were overlooked by the radiologist, and three probably would have been seen if small-bowel roentgen studies had been requested.

Treatment and Results

In most cases the reason for performing an operation was roentgen evidence of a tumor. However, nine patients in this series were operated upon for other reasons. In two (cases 10 and 12) acute small-bowel obstruction was the immediate reason for operation, although both patients had for some time had symptoms suggesting intermittent small bowel obstruction. In four (cases 26, 27, 30 and 31) celiotomy was done because of recurrent severe intestinal bleeding. All of these patients had careful roentgen studies which showed no abnormalities. In case 11 adenocarcinoma of the jejunum was found during an operation for duodenal ulcer, although the tumor was the more likely cause of the symptoms. In case 23 the lymphosarcoma of the ileum was found at the time of splenectomy, although the patient had been having attacks of abdominal pain which were probably caused by the

TABLE 3

Operative Findings and Procedures and Results of Treatment

Case	Metastases*	Operative Procedure	Delay in Diagnosis†	Survival after Operation
Adenocarcinomas				
1	0	None‡	16 months	—
2	+	Celiotomy and biopsy	7 months	10 days
3	0	Resection	14 months	30 months§
4	+	Resection	36 months	2 weeks
5	0	Resection	3 months	12 months
6	+	Celiotomy and biopsy	24 months	Unknown
7	0	None‡	1 week	—
8	+	Resection	6 months	12 months
9	+	By-pass enterostomy and biopsy	22 months	5 months
10	0	Resection	18 months	7 years§
11	+	Resection	4 months	12 months
12	0	Resection	6 months	7 years§
13	+	Resection	9 months	11 months
14	0	Resection	6 months	6 years
15	+	Celiotomy and biopsy	10 months	3 months
16	+	None‡	10 months	—
17	+	None‡	17 months	—
Carcinoids				
18	+	By-pass enterostomy and biopsy	24 months	26 months
19	+	Resection	6 months	6 months§
Sarcomas				
20	+	Resection	12 months	8 years
21	+	Celiotomy, biopsy, and closure of perforation	3 months	2 days
22	0	Resection	6 weeks	15 years§
23	0	Resection	6 months	7 years
24	+	Resection	3 months	5 years
25	0	Resection	1 month	1 year§
26	0	Resection	5 years	8 years§
27	0	Resection	30 months	8 years§
Benign tumors				
28		Resection	20 months	18 months§
29		Resection	2 weeks	5 years§
30		Resection	11 months	18 months§
31		Resection	24 months	4 months§
32		Resection	6 months	5 years§

* Metastases found at initial operation, or at autopsy if no operation was performed.
† Time from first symptoms until diagnosis made.
‡ Autopsy provided the diagnoses in these cases.
§ Alive.

tumor. In case 21, which has already been described,[6] the operation was for acute perforation of a lymphosarcoma of the jejunum.

Table 3 lists the important features of the operative findings and procedures, as well as the time of delay in diagnosis and survival time after operation. At the time of operation (or autopsy, in the cases where an operation was not performed) there was evidence of metastases (local or distant) in 15 of the 27 patients who had malignant tumors. Four patients

did not have operative procedures, and the diagnosis was made or confirmed at necropsy.

Twenty-two patients had a resection of the involved segment of bowel and of local metastatic lesions if present. Two had an entero-enterostomy to by-pass the area of the tumor and a biopsy of the tumor, while four had celiotomy and a biopsy of the tumor or its metastases.

FIG. 1. *Case 5.* Adenocarcinoma of the jejunum. Note the dilated, barium-filled small bowel loops.

None of the patients with adenocarcinoma who had metastases at operation survived more than 12 months; of the seven patients with localized adenocarcinomas, two died without having an operation, three survived five years or more, and two of these are alive seven years after operation.

One patient with lymphosarcoma of the jejunum was operated upon because of a perforation at the site of the tumor and died two days later of peritonitis. The other seven patients with sarcomas or lymphosarcomas had a resection of the tumor. Three survived five, seven and eight years before death, and the other four are still alive from one to 15 years after resection.

All of the five patients with benign tumors are still alive four months to five years after operation.

Comment

From the point of view of the clinician, the roentgenologist found 20 tumors and missed the lesion in only five cases where small-bowel studies were requested. The tumor was found in a number of cases because of the alertness of the radiology department in recognizing the tumor at the time of an ordinary gastrointestinal roentgen study, and not because the clinician directed attention to this possibility. If the clinician recognizes

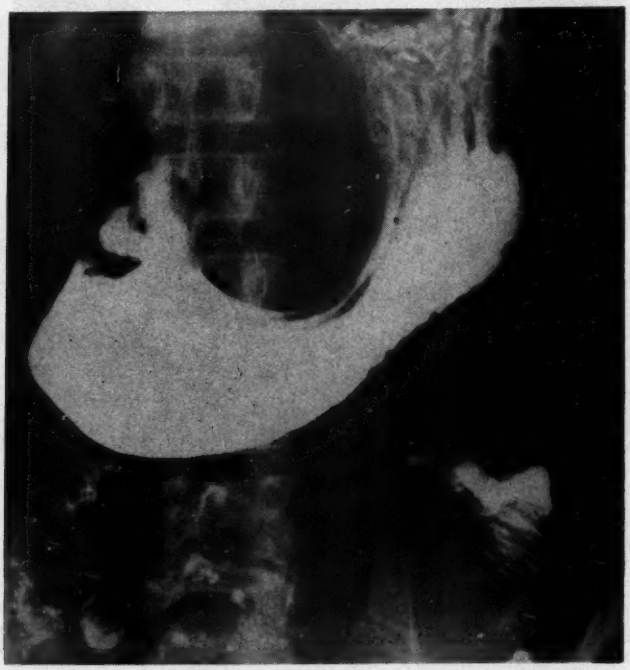

FIG. 2. *Case 6.* Adenocarcinoma of the jejunum. A survey film taken 90 minutes after routine upper gastrointestinal series shows traces of barium in the upper jejunum outlining an abnormal mucosal pattern.

the clinical patterns described and directs the attention of the radiologist to the proper area, earlier diagnoses should be possible. If, in the presence of these clinical patterns, careful roentgen studies of the small bowel do not show an abnormality, exploratory celiotomy must be seriously considered.

Case Reports

Case 5. Adenocarcinoma of the Jejunum—Obstruction Pattern: A 40 year old woman entered the hospital because of abdominal pain. Three months before admission she had begun to have attacks of severe, crampy, periumbilical pain which radiated to the groins and lasted from 30 minutes to several hours. The attacks were

accompanied by nausea and vomiting, and occurred at 10-day intervals. Two weeks before admission she began to have abdominal cramps and diarrhea. She had a 16-pound weight loss during the illness. Physical examination revealed a mass posterior to the uterus. Laboratory studies showed normal hemoglobin levels and no occult blood in the stools. Barium enema showed only a few diverticula. Upper gastrointestinal roentgen series was negative except that a 24-hour film showed dilated loops of small bowel. Small bowel series (figure 1) showed marked retention of barium in the small-bowel loops, although no lesion was seen. A diagnosis

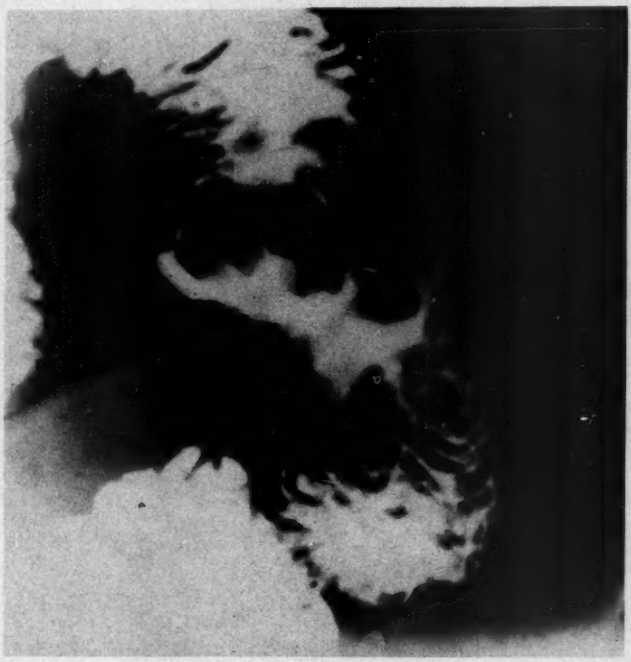

FIG. 3. *Case 6.* Adenocarcinoma of the jejunum. Spot film taken during small bowel study, showing an ulcerated nodular segment of upper jejunum at the suspected location.

of small-bowel obstruction was made. At operation there was a constricted area completely encircling the jejunum six inches below the ligament of Treitz. This area of jejunum was resected and there was no evidence of metastases. At reoperation eight months later there were extensive mesenteric and liver metastases.

Case 6. Adenocarcinoma of Jejunum—Blood Loss Pattern: A 49 year old woman was examined because of anemia. About two years before admission she had become weak, and one week later had fainted. She was admitted to a hospital, where her hemoglobin level was found to be 35% of normal. An upper gastrointestinal roentgen series was reported to be normal. Treatment with iron and liver resulted in improvement, but she continued to be anemic. For an unspecified period of time she had intermittent right thoracic pain associated with epigastric discomfort and nausea, lasting one to two hours after meals. She had gained weight during her illness. Physical examination disclosed only pallor. The hemoglobin was 37% of

normal, and the blood smear showed marked hypochromia. The stools contained occult blood by guaiac test. During the period of examinations she began to have crampy, midabdominal pain frequently during the day. Upper gastrointestinal roentgen series showed a hiatus hernia, and on one film, taken two hours after the intake of barium, there were peculiar deposits of barium in one loop of the small bowel (figure 2). A later study was limited to this area and showed (figure 3) a 6 cm. length of jejunum that was ulcerated. At operation there was a 12 cm. mass in-

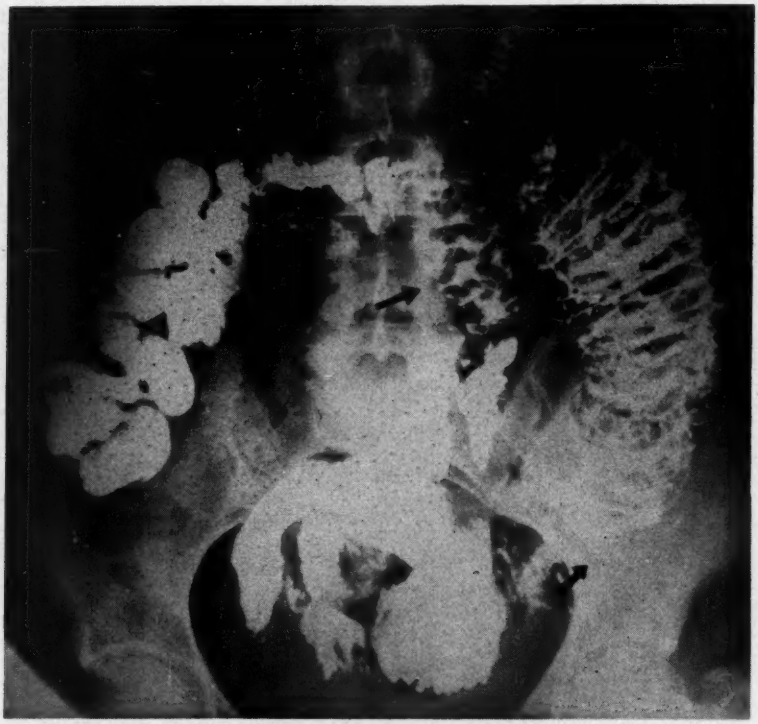

FIG. 4. *Case 20.* Lymphosarcoma of the jejunum. Note the two dilated loops of jejunum in which there is coarse distortion of the mucosal pattern.

volving the jejunum six inches beyond the ligament of Treitz. The transverse and descending colon were adherent to the mass which, on examination, showed adenocarcinoma.

Case 20. Lymphosarcoma of the Jejunum—Obstruction Pattern: A 43 year old woman was admitted to the hospital because of abdominal pain. One year before admission she had had a single attack of severe, crampy, generalized abdominal pain which lasted for one hour and was relieved by vomiting. She was then well until five weeks before admission, when she began to have repeated attacks of the same pain, accompanied by vomiting. She lost 18 pounds. An abdominal mass was felt at times on the right, at others on the left side of the abdomen. The hemoglobin was 9.9 gm./100 ml., and a stool specimen showed occult blood by guaiac test. Upper gastrointestinal roentgen studies showed changes in two segments of the upper

jejunum (figure 4) which measured 15 by 6.5 cm. and 6.0 by 3.5 cm. In these areas the lumen was greatly enlarged, and Kerckring's folds were rigid and widened but had an arrangement similar to the normal. At operation, a four-foot segment of jejunum was resected and showed one 14 cm. length and several shorter segments in

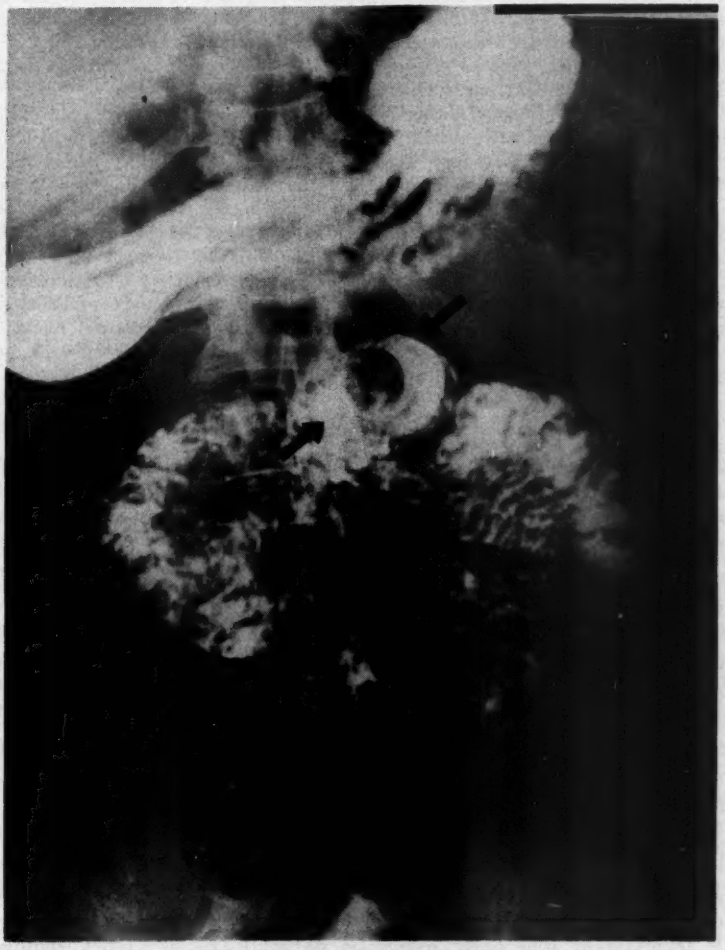

FIG. 5. *Case 29.* Neurofibroma of the jejunum. A round filling defect is seen on follow-up film after upper gastrointestinal series.

which the wall was thickened and coarsely corrugated. Microscopic examination showed lymphosarcoma. The patient lived for eight years, during which time x-ray therapy and another resection of tumor provided palliation.

Case 25. Lymphosarcoma of Ileum—Obstruction Pattern: For three or four weeks this 24 year old man had intermittent epigastric pain and generalized crampy abdominal pain two to three hours after breakfast. This was relieved by an ulcer

regimen. On the afternoon before admission an upper gastrointestinal roentgen series was done and during this he began to have severe upper abdominal pain and vomiting. These symptoms subsided but recurred on the following day, when his abdomen was slightly distended. There was a firm 8 cm. mass in the right lower quadrant. Peristalsis was decreased. The hematocrit was 50% and the leukocyte count was 20,200 (90% polymorphonuclears). A plain film of the abdomen showed barium in multiple, dilated small-bowel loops. At operation there was a 15 by 20 cm. mass of intussuscepted ileum extending almost to the cecum, the leading point of which was a lymphosarcoma measuring 1.5 by 0.5 cm.

Case 29. Neurofibroma of Jejunum—Blood Loss Pattern: A 56 year old man had been entirely well until two weeks before admission, when he began to have tarry bowel movements and became very weak. A roentgen study before admission was said to have shown a duodenal deformity. Physical examination showed only pallor. The hemoglobin level was 8.0 gm./100 ml., and the stools were positive for occult blood by guaiac test. An upper gastrointestinal roentgen series revealed a filling defect in the region of the ligament of Treitz. Small-bowel roentgen series showed a 5 cm. smooth tumor mass in an upper loop of jejunum (figure 5). At operation a 5 cm., dark red vascular mass in the jejunum was resected, and proved to be a neurofibroma. The tumor was subserosal but projected into the bowel lumen, and there were two small ulcerations on its surface. The patient has been well during the five years since operation.

Summary

The records of 32 patients with primary symptomatic small-bowel tumors were studied in an attempt to define the clinical pattern produced by these tumors. Most patients had a pattern either of obstruction with attacks of crampy abdominal pain, or of blood loss characterized by intermittent severe bleeding in the benign tumors, and anemia and occult blood in the stools in the malignant tumors.

Roentgen studies showed the tumor in 18 of 29 cases studied with contrast media, and led to the diagnosis in two other cases by disclosing evidence of obstruction. Three of the nine tumors which were not seen by the radiologist were located primarily extraluminally and probably could not have been seen. Another three would have been visible if small-bowel roentgen studies had been requested. The final three were overlooked by the radiologist.

Twenty-nine patients had an operative procedure, and metastases (local or distant) were found in 15. Three patients who had adenocarcinoma of the jejunum survived for more than five years, while seven of eight patients who had sarcoma are either living or survived more than five years.

It is apparent that early diagnosis of small-bowel tumors requires a clinician alert to the clinical patterns, and a radiologist aware of the roentgen abnormalities which may be produced by these tumors.

Summario in Interlingua

Tumores del intestinos tenue es rar e difficile a diagnosticar. Pauc articulos in le litteratura se concerne primarimente del configurationes clinic initial in casos de tal tumores.

Le dossiers de 32 patientes con primari tumores symptomatic del intestinos tenue esseva studiate con le objectivo de definir le configurationes clinic de iste tumores. Vinti-septe del patientes habeva tumores maligne: 17 adenocarcinomas (duo del duodeno, 14 del jejuno, un del ileo), duo carcinoides, cinque lymphosarcomas, un lymphoma, un fibrosarcoma, e un leiomyosarcoma. Inter le cinque benigne tumores, duo esseva adenomas e le remanente tres esseva un lipoma, un neurofibroma, e un hemangiopericytoma.

In le majoritate del casos, le signos e symptomas congrueva con un de duo schemas clinic. Le prime—le configuration de *obstruction*—esseva characterisate per episodic dolores crampiforme del abdomine. Isto esseva prominente in 13 casos. Le secunde configuration principal—illo de perdita de sanguine—occurreva in 13 patientes. Le patientes con tumores benigne habeva frequentemente sever hemorrhagias manifeste in debilitate, melena, e anemia, durante que le patientes con tumores maligne habeva usualmente constante sanguination occulte. In sex casos, altere configurationes clinic esseva notate: Duo habeva febre solmente, un le syndrome de rubor de carcinoide, e tres continue dolores abdominal.

Studios roentgenographic con barium esseva effectuate in 29 casos. In 18 le tumor esseva visualisate; e in duo alteres, signos de obstruction in le intestino tenue indicava le correcte diagnose.

Tres del nove tumores non vidite per le roentgenologo esseva locate primarimente extra le lumine e ergo non poteva esser vidite. In tres altere casos, le clinico non demandava studios roentgenologic del intestino tenue, e le serie supero-gastrointestinal routinari non permitteva le visualisation del area in que le lesion esseva presente. Le ultime tres casos escappava al vigilantia del roentgenologo.

Vinti-nove del patientes esseva subjicite a operationes. Metastases esseva trovate in 15. Tres patientes qui habeva adenocarcinoma del jejuno superviveva plus que cinque annos; septe del octo con lymphoma o sarcoma vive ancora o superviveva al minus cinque annos.

Tumores del intestino tenue causa usualmente characteristic configurationes clinic. In le caso individual—si nulle altere causa de un de iste configurationes es obvie e si le usual studios roentgenologic del vias gastrointestinal non demonstra un causa pro le symptomas—le clinico debe diriger le attention del roentgenologo al intestino tenue. Le majoritate del tumores pote esser trovate per simple studios roentgenologic del intestinos tenue, sed in un numero restringite de casos le tumor non es visualisabile e un operation exploratori es indicate.

BIBLIOGRAPHY

1. Botsford, T. W., and Seibel, R. E.: Benign and malignant tumors of the small intestine, New England J. Med. **236**: 683–694, 1947.
2. Shallow, T. A., Eger, S. A., and Carty, J. B.: Primary malignant disease of the small intestine, Am. J. Surg. **69**: 372–383, 1945.
3. River, L., Silverstein, J., and Tope, J. W.: Benign neoplasms of the small intestine, Internat. Abst. Surg. **102**: 1–38, 1956.
4. Pridgen, J. E., Mayo, C. W., and Dockerty, M. B.: Carcinoma of the jejunum and ileum exclusive of carcinoid tumors, Surg., Gynec. and Obst.: **90**: 513–524, 1950.
5. Jeghers, H., McKusick, V. A., and Katz, K. H.: Generalized intestinal polyposis and melanin spots of the oral mucosa, lips and digits, New England J. Med. **241**: 993–1005, 1031–1036, 1949.
6. MacMahon, H. E., Aisner, M., and Patterson, J. F.: Reticulum cell sarcoma simulating miliary tuberculosis, Bull. New England M. Center **16**: 42–51, 1954.
7. Irvine, W. T., and Johnstone, J. M.: Lymphosarcoma of the small intestine, Brit. J. Surg. **42**: 611–618, 1955.

8. Lingley, J. R.: Non-obstructing malignant tumors of the small bowel. A report of five cases, Am. J. Roentgenol. **36**: 902–909, 1936.
9. Root, J. C.: Roentgenologic diagnosis of tumors of the small intestine, M. Clin. North America **32**: 436–442 (Mar.) 1948.
10. Good, C. A., and Fletcher, M. E. H.: The roentgenologic examination of the small intestine, J. M. A. Georgia **37**: 67–74, 1948.
11. Dundon, C. C.: Primary tumors of the small intestine, Am. J. Roentgenol. **59**: 492–504, 1948.
12. Maxwell, E. A., Crile, G., Jr., and Dinsmore, R. S.: Malignant tumors of the small intestine, S. Clin. North America **28**: 1149–1157 (Oct.) 1948.
13. Hodes, P. J., and Edeiken, J.: Roentgen manifestations of small intestinal bleeding, J. A. M. A. **141**: 1284–1290, 1949.
14. Perry, S. P., and Haden, W. D., Jr.: Primary malignancy of small intestine, Guthrie Clin. Bull. **16**: 79–87, 1947.
15. Weber, H. M., and Kirklin, B. R.: Roentgenologic manifestations of tumors of the small intestine, Am. J. Roentgenol. **47**: 243–253, 1942.
16. Keats, T. E., and Sakai, H. Q.: An evaluation of the sources of error in the roentgenologic diagnosis of neoplasms of the small intestine, Gastroenterology **29**: 554–562, 1955.

PHYSICAL MEDICINE AND REHABILITATION: EFFECTIVENESS AND PROGRESS IN RESTORATION OF THE CHRONICALLY ILL AND AGING *

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THE population of the United States is aging and, associated with this fact, serious long-term illness is becoming an increasing threat to our nation's health. Advances in medical science, improved surgical methods, new drugs, scientific nutrition, decrease in infant mortality, the diminishing toll of infectious diseases, and better public health measures and other medical accomplishments have advanced life expectancy by many years. There is every reason to believe that this will continue.

The average life span has increased from 47 to 68 years during the last half-century. By 1970 it is estimated there will be about 17 million persons 65 years of age or over.

The Veterans Administration has been deeply concerned with the complex problems of the chronically ill and aging, since the number of veterans in these categories compares closely with the percentage in the general population. With reference to the ages of veterans in hospitals, a census of patients remaining in Veterans Administration hospitals on November 30, 1955, indicated that, of 112,064 patients, 15,084 were over 65 years of age.[1] The increase in average age is even more marked among veterans in domiciliaries than among hospitalized patients. On June 30, 1956, there was an average daily member load of 16,814 in Veterans Administration domiciliaries, and the average age of these veterans was 62.2 years. As of July 1, 1955, there were 21,878,000 veterans, of whom 698,000 were 65 years of age or over. By the year 1985 it is estimated there will be 4,508,000 veterans 65 years of age or over.

Two surveys of the number of long-term patients in all Veterans Administration hospitals have been completed, one in 1955 and one in 1956. It was found that their number had increased from over 8,000 in 1955 to over 10,000 in 1956, in spite of the fact that more than 800 of these older veterans had died in the interim.[2] It is therefore apparent that we must concentrate as fully on the treatment and rehabilitation of these patients as we do on the acutely ill if we are to alleviate this growing challenge.

It has been firmly established that physical medicine and rehabilitation provides essential and valuable consultation and treatment services to all

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other medical specialties in the coördinated and total team approach toward treatment and rehabilitation of the whole man. This has been especially true with reference to the acutely ill and the severely disabled. Now physical medicine and rehabilitation is making a definite contribution to the restoration of chronically ill and geriatric patients. In many instances the application of the principles and procedures of physical medicine and rehabilitation for the prevention, diagnosis, treatment and rehabilitation of long-term and geriatric illness and disability has produced dynamic results." [3]

The Chief of the Physical Medicine and Rehabilitation Service is Chairman of the Medical Rehabilitation Board, which serves as an overall coordinating body for planning for patients with severe and complex rehabilitation problems. Evaluation clinics similarly pin point the professional skills of hospital personnel on these patients for planned and graduated rehabilitation regimens.

"In physical medicine and rehabilitation we insist that each member of the rehabilitation team—the coördinator (executive assistant), therapists of the various categories, the clinical psychologist, social worker, and vocational counsellor—exert every effort and utilize every ingenious device to motivate the patient, and thus constantly perpetuate the patient's interest in his own recovery and restoration to independence. This technique may demand the establishment of competitive elements among the older patients, each one striving to outdo the other, but always under careful medical supervision. We must assist the patient in setting realistic goals for himself and to make practical and feasible plans for accomplishing them." [4]

In physical medicine and rehabilitation there are numerous specific measures which may be utilized in the definitive treatment of disease and disability of almost every category and degree. This has been amply demonstrated for many years, but especially since World War II. Our colleagues in the specialties of internal medicine, surgery, neurology, psychiatry, pediatrics and chest diseases rely on the physiatrist for procedures in his armamentarium to help their patients as a part of the active therapeutic regimen in acute illness. This applies to chronic illness and to illness in old people as well as to illness in the younger age groups. We know that motivation, hope for the future, return of self-respect and restoration of confidence are even more important in these patients, and these factors can often be instilled by the dynamics of physical medicine and rehabilitation.

The greatest utilization of physical medicine and rehabilitation is naturally in the specific area of rehabilitation for the chronically ill and aging. In speaking of the restoration of these patients to jobs, Rusk [5] stated: "Lacking specific measures for the cure of many of the diseases which produce this tremendous load of disability, medicine must look to rehabilitation for the 'restoration of the handicapped to the fullest physical, mental, social, vocational and economic usefulness of which they are capable.' "

Complete treatment and restoration of these patients require that adequate rehabilitation services be available. At times, properly prescribed

physical medicine and rehabilitation may correct a disability entirely, being usually most helpful in restoring function in whole or in part. Again, with appropriate measures in this field, the progression of disease or disability may be retarded or halted. We must not overlook the great value of these modalities in restoring many of these patients to the point of self-care, or to full or part-time employment.

We have a physical medicine and rehabilitation bed service in many of our hospitals, and this has proved to be of considerable help in providing intensive rehabilitation for long-term and aged patients who are referred to the physiatrist by consultation. When he accepts them for his ward they become his direct responsibility, and usually the resulting more concentrated therapy has been effective in enabling the patient to look forward to discharge from the hospital and return to his home, frequently to partial or full-time employment. This is demonstrated by a report from the Veterans Administration Hospital at Fort Howard, Maryland, where 53 patients who were destined to remain in the hospital for the rest of their lives were able to leave the hospital. After an end-of-year follow-up study, none of them had returned to the hospital for extended hospitalization.

Thus, one readily sees that the preventive, definitive and maintenance aspects of physical medicine and rehabilitation are of paramount importance in overcoming the challenge of chronic illness and aging. Adequate evaluation of the patient, careful reëvaluation as necessary, reconditioning procedures within physical tolerance, activities of daily living including self-care, appropriate rehabilitation counseling, establishment of feasible and ultimate objectives for rehabilitation, and medical guidance for selective placement in employment, when indicated, are all important facets of this work. Although progress in recent years in physical medicine and rehabilitation as applied to chronic illness and geriatric problems has been favorable, we in this specialty are aware of the enormous task which faces all of us in medicine. We hope to contribute, on a team basis and in a coordinated and total approach, to further accomplishment in this field. We are acutely aware of the vital importance of painstaking research and continuous study of these problems—for example, the definition, measurement and evaluation of senescence. Similarly, there must be investigation of the common factors in several of the chronic diseases, the role of hereditary factors, and the influence of emotional and environmental factors.

It should be possible to alleviate the general deterioration and gradually declining vitality of the older person. It is logical to state that the senior citizen may rightfully anticipate further life and fuller living with increasing age, rather than curtailment of activity and diminishing productivity. As Robert Browning said,

Grow old along with me!
The best is yet to be,
The last of life, for which the first was made.

Motivation of the patient is necessary if he is to be restored to usefulness, yet it is frequently most difficult to stimulate. However, overmotivation must be avoided. The patient must not be stimulated to exert himself beyond his physical, mental or emotional tolerance.

Resocialization of the patient and his subsequent reintegration into family and community life are most vital to successful rehabilitation. The accomplishment of these factors requires unanimity of purpose, thought and understanding of all members of the rehabilitation team.

Frequently, in the rehabilitation of the chronically ill and aging, it becomes necessary to adapt, devise or modify present equipment and current technics in order to bring about effective and early restoration of the patient. Assistive devices of all types are utilized to help the patient, which are changed when necessary to conform to his improved status, and which perhaps he will not need at a later stage in his progress.

Rehabilitative maintenance therapy is essential in the care of many chronically ill patients. This is a schedule of minimal activity or exercise required to maintain at maximal feasible level the physical status of the patient with a poor prognosis for ultimate improvement. Rosenberg et al.[6] stated: "This objective is usually established for the patient by the physiatrist under the following conditions: (1) after the patient has undergone intensive restorative therapy and has reached the point of maximum treatment benefit, and it appears likely that he cannot maintain his own physical condition; (2) where a geriatric patient has deteriorated in the absence of physical medicine and rehabilitation therapy, and maintenance therapy is necessary to prevent contractures, disuse atrophy, decubiti, incontinence, weakness of musculature, and loss of self-care ability."

An efficient follow-up system is important after discharge of the patient to insure that he has fully achieved and is maintaining the goal planned for him. If circumstances at any time indicate that he cannot sustain this level of accomplishment, immediate steps must be taken to prevent further relapse and need for hospitalization. This can often be realized by rehabilitation therapy on an outpatient basis.

Preventive physical medicine and rehabilitation include, therefore, those measures which avert the occurrence of more serious or complex disability, and those which may halt or retard such progression of the disease process as to cause increased disability, deconditioning or deterioration.

There is a great challenge in this total problem for broad and effective education in order to promote better understanding of the importance of health maintenance, positive rehabilitation, and community reintegration for our aged and chronically ill citizens. These health educational measures should be realistic, factually sound, and directed to orient health workers, families, industry and the public with reference to these problems.

The progress we have made to date in physical medicine and rehabilitation in helping to solve this vast problem forms a firm foundation from which

to plan and project future strategy for more efficient operation and even more effective results. We must together develop greater possibilities for the aging and chronically ill in our economy, in our society, and in our industrial world. Reinartz [7] stated: "Medical science has added years to the average life of our people, but we have thus far not met the challenge of teaching the elderly to live as socially useful individuals. Emphasis in this young country has been on youth and production. We have, up to this time, dwelt on the infirmities and limitations of the older individual, rather than on his remaining and very real capabilities. Now, we have been made increasingly aware of the impact of this mounting array of millions of people over the age of 65."

At the Veterans Administration Center, Los Angeles, a report [8] showed that from April, 1951, to July, 1953, a total of 127 older veterans had been discharged to home and a job; from August, 1953, to May 1954, 196 veterans were discharged to home and a job; the former number was from 719 patients evaluated, the latter from 1,347 patients evaluated. The report stated further: "The present domiciliary member population can probably best be described as a relatively static, chronically ill, predominantly male group of individuals with a mean age of approximately 63 years. Approximately 2,000 veterans admitted consecutively for domiciliary care were personally interviewed by the Assistant Chief, and Executive Assistant, of the Physical Medicine and Rehabilitation Service. This group in particular is mentioned because they present the most difficult, perplexing and frustrating problems in this type or any type of program. It is our opinion, after seeing approximately 300 of these individuals over a three and a half-year period, that the big majority of them are severely disabled. The problems presented by these members show the basic need for more knowledge of these individuals."

The numerous observations made in the above study bear out the basic principles which have been established in the treatment and rehabilitation of the aged and chronically ill, including the importance of early referral of these patients to the Physical Medicine and Rehabilitation Service.

Physical medicine and rehabilitation have likewise been able to make a similar contribution in the rehabilitation of many other categories of patients, including the blind, cardiacs, hemiplegics, paraplegics, other neurologic patients, tuberculous patients and psychiatric patients. The attitude of hospital management to this contribution was illustrated by Timm,[9] manager of a psychiatric hospital, when he stated: "To summarize, it may be said that, insofar as the psychiatric hospital is concerned, the role of physical medicine and rehabilitation is to provide all of those services which are ordinarily provided in the general hospitals for the improvement of function, for the bringing about of fuller and more complete recovery, but, uniquely in the mental hospital, its role is to provide the main therapeutic approach to chronic mental illness, and that, properly oriented with a properly trained

staff, the problems of chronic illness can be attacked rationally with the resources that we now have."

The task we face in the health, rehabilitation and employment problems of the aging and chronically ill will continue to increase in complexity, degree and scope. Instead of a hopeless or passive attitude, we must develop a feeling of hope, optimism and reassurance, and apply them in a dynamic and positive approach toward the problem. An aggressive and unrelenting attack must be instituted through adequate and complete physical medicine and rehabilitation services working in close coöperation and harmony with the rest of the medical profession.

This over-all problem of aging and chronic long-term illness is not a series of separate entities which can be overcome one by one, but is instead a complex of related problems which demand coördinated and united solution. Working together, we can achieve effective and progressive action to meet and liquidate this challenge of aging and chronic illness.

SUMMARIO IN INTERLINGUA

Como resultato de numerose progressos in le scientias medical, le population del Statos Unite augmenta continuemente su etate, con le resultato de un semper plus grande numero de citatanos de etate avantiate qui es invalidate per morbos chronic de varie typos e de varie grados de severitate. Le Administration de Veteranos es profundemente concernite con le complexitates de iste problema, proque le numero del veteranos in le categorias del chronicamente malades e invetulates es plenmente comparabile al correspondente procentages in le population general. Le numero del veteranos calculate pro le 1 de julio 1955 esseva 21.878.000, e iste total includeva 698.000 con etates de 65 annos o plus. On estima que in 1985 le numero de veteranos de etates de 65 annos o plus va esser 4.508.000.

Un Servicio de Medicina e Rehabilitation Physic ha essite instituite como un del major servicios in omne hospitales del Administration de Veteranos, con le function de provider servicios essential e profitabile de consultation e de tractamento pro omne le altere specialitates medical, de accordo con le conception de un coordination e cooperation comprehensive inter omne le fortias concernite con le tractamento e le rehabilitation del veteranos malade e invalide.

Iste Servicio servi le patientes in le clinica de rehabilitation pro patientes visitante, in le salas del altere servicios medical, e, le plus intensemente, in le salas de rehabilitation. In omne isto, le objectivo primari es retornar le veterano a su domicilio, su familia, e su empleo, in tanto que isto es del toto possibile.

Factores de importantia primari in iste effortio es le evalutation adequate del patiente, un meticulose re-evalutation si necessari, procedimentos de reconditionation intra le limites del tolerantia physic, le recommendation de activitates in le vita quotidian que re-establi le independentia del patiente, appropriate consiliation in le problemas del rehabilitation, e surveliantia e direction medical in le selection de empleos in tanto que possibile. Un adequate motivation del patiente es essential si on vole que ille es restaurate a un vita de successo e utilitate.

Le therapia "de mantenentia" consiste de un programma de activitate minimal que es requirite pro mantener le stato physic specialmente de patientes con pauco favorabile prognoses.

Un efficace systema de surveliantia consecutori post le dimission del patiente es indispensabile. In certe casos, mesuras immediate debe esser prendite pro evitar

recidivas. Therapia rehabilitational con le patiente visitante o re-hospitalisate pote esser necessari.

Un studio effectuate al Centro del Administration de Veteranos a Los Angeles in California ha demonstrate le contribution facite per le Servicio de Medicina e Rehabilitation Physic in le restauration de patientes de etates avantiate qui es chronicamente malade e invalide. Le resultante economias financiari in le costos del hospitalisation es un factor multo significative.

BIBLIOGRAPHY

1. Committee on Labor and Public Welfare, United States Senate: Care of the aging by the Veterans Administration (Selected Documents—Volume VI), Washington, D. C., U. S. Government Printing Office, Nov., 1956, p. 92.
2. Knudson, A. B. C.: Rehabilitation of the chronically ill in the Veterans Administration, J. A. M. A. **162**: 1035 (Nov. 10) 1956.
3. Knudson, A. B. C.: Physical medicine and rehabilitation: application in geriatrics, Southern M. J. **50**: 229 (Feb.) 1957.
4. Knudson, A. B. C.: Physical medicine and rehabilitation: application to geriatric problems, J. Am. Geriat. Soc. **2**: 566 (Sept.) 1954.
5. Rusk, H. A.: Can older persons be rehabilitated for work? *in* Never too Old, New York State Joint Legislative Committee on Problems of the Aging, 1949, p. 126–131.
6. Rosenberg, L., Matheny, W. C., and Randall, B. S.: Geriatric maintenance therapy program, Department of Medicine and Surgery Information Bull. Vet. Adm., p. 14 (Feb.) 1955.
7. Reinartz, P. V.: Retirement plans, J. Am. Geriat. Soc. **1**: 829 (Dec.) 1953.
8. Haase, K. H.: The special challenge for physical medicine and rehabilitation in a domiciliary section at a VA Center, VA Information Bulletin, Physical Medicine and Rehabilitation Service, IB 10-72 (Feb.) 1955, p. 3.
9. Timm, O. K.: The role of physical medicine and rehabilitation in the neuropsychiatric hospital, VA Program Guide, Physical Medicine and Rehabilitation Service, G-5, May 15, 1956, p. 1.

CASE REPORTS

DIPHTHERITIC MYOCARDITIS WITH PERMANENT HEART DAMAGE *

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Acute myocarditis is a common complication of diphtheria and is said to occur in from 10 to 25% of cases and to be responsible for from 50 to 60% of the deaths from this disease.

Pathologic changes consist of fatty and hyaline changes in heart muscle, sometimes associated with necrotic changes or toxic myolysis in muscle fibers. Interstitial changes also occur, consisting of edema and infiltration with lymphocytes, neutrophilic and eosinophilic leukocytes, monocytes and fibroblasts.

It seems rather extraordinary that, despite the clinical severity of many cases of acute diphtheritic myocarditis and the widespread pathologic damage reported, it is seldom possible to trace any permanent cardiac damage.

White et al.[1] followed 100 individuals who had had severe diphtheria for 10 years, and 90 of them for a further 10 years, and none showed any evidence of heart disease. Paul White wrote: "One may therefore conclude that chronic diphtheritic heart disease is notable for its rarity. Unlike rheumatic fever and syphilis, diphtheria is not a long drawn out, progressive infection which may cause a delayed cardiac effect; rather the reverse is true."

At the end of an excellent discussion of the heart in diphtheria, Friedberg[2] reached this conclusion: "That diphtheritic myocarditis may lead to permanent fibrosis which predisposes to cardiac enlargement and congestive heart failure much later in life has been suggested but remains unproven."

Wood,[3] in his *Diseases of the Heart and Circulation,* says emphatically: "If the patient survives, the ultimate prognosis is excellent and complete recovery may be promised without reserve. It is important that the patient should be convinced of this from the start, in order to prevent anxiety neurosis and to maintain good morale."

In 1952 Griffith and Herman[4] reported an interesting case of a woman who, following an attack of diphtheria, survived for 12 months with permanent conduction defects and congestive failure. At autopsy a small amount of fibrosis was found in the subendocardial region of the left ventricle, and it was assumed that death was a direct sequel of diphtheria.

In 1953 Hoel and Berg[5] reported on 162 patients who had shown clinical signs of heart disease or electrocardiographic changes during the acute stage of diphtheria. The patients had been studied from five to eight and one-half years after infection. None showed congestive heart failure. One, however, had a

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marked disorder of the heart, with attacks of vertigo caused by alternating heart block. Seventeen had various electrocardiographic abnormalities, probably of diphtheritic etiology:

Six with prolonged conduction time.
Three with bundle branch block.
One with bundle branch block and complete heart block.
One with Wilson block.
Six with depression of the ST segments or change in the T waves in the first two limb leads.

In two of these 17 patients, the heart disease had taken a subacute course with varying symptoms for several years.

This paper suggests that permanent cardiac damage may sometimes occur as a result of diphtheria, but that damage of clinical severity is rare.

In view of this generally accepted opinion, I felt that the following case history is worth relating.

Case Report

Before enlistment this man had been a noted New Zealand athlete. He had represented his country at cricket as a wicket-keeper and his University as a footballer. He was a good tennis player and an excellent golfer. For some years before enlistment he had done very hard physical work. Friends who knew him in those days report that he made almost a fetish of physical fitness.

On June 10, 1940, at the age of 27, he was examined for overseas service and was passed as grade 1 (fit for service in any part of the world). His records show that no abnormality was found on physical examination. His heart was clinically normal, his blood pressure was 120/85 mm. of Hg, and his cardiac efficiency test was normal. No electrocardiogram was taken. There was no history of previous illness.

In January, 1941, he entered camp for training, and on April 7, 1941, he left New Zealand for overseas and entered Egypt on May 17, 1941. There is no record of any illness till February 9, 1942, when he was admitted to a New Zealand General Hospital.

One week before admission he had developed symptoms suggestive of a common cold. Three days before admission he developed a sore throat with headache, anorexia and constipation. Two days before admission edema was noticed around the left eye.

On admission the left tonsil was enlarged and inflamed, with exudate present; the right was also swollen, with a little exudate. Both tonsillar glands were palpable and tender. No abnormalities were detected in any other system.

A throat swab was sent to the laboratory and was reported as "negative for K.L.B." The predominating organisms were streptococci.

The patient was treated with antistreptococcal serum, which was repeated on the following day, and also with sulfapyridine.

On February 12, 1942, both tonsils were covered with a sloughing membrane, and there was also membrane in the left nostril. There was a brawny swelling of the left infra-orbital region. He was placed on the "seriously ill" list. On this day a nasal swab was sent to the laboratory and the report was as follows: *"Culture:* a heavy growth of bipolar staining bacilli morphologically resembling but not typical of K.L.B. Organisms being subcultured biochemically."

Six days later, on February 18, 1942, a further report on this culture stated: "Biochemical reactions confirmed this organism as *Corynebacterium diphtheriae.*"

Over the next four days there was steady improvement in his general condition. The edema of the face decreased and the throat improved. On February 16 he was taken off the "seriously ill" list. On February 24, 15 days after his admission to hospital, a nasal swab was reported as "positive for K.L.B." On March 9, one month after admission, some exudate was noted on the left tonsil, but it is reported that there had been three negative swabs for *C. diphtheriae*.

On March 12 there were symptoms suggestive of myocardial involvement, and an electrocardiogram confirmed this. Over the next few weeks his pulse rate was 50 and of poor volume, and he complained of dyspnea. He was kept at absolute rest and was fed and washed.

At this time he developed diplopia and blurring of vision. It is stated that it developed in the fifth week of his illness and lasted for from four to five weeks. He also developed severe peripheral neuritis, with weakness of arms and legs and absent deep reflexes.

Recovery was slow but steady, and on June 18, 1942, the patient was discharged to a rest home after 18 weeks in hospital. He spent seven weeks convalescing and was then discharged.

On October 1, 1942, the patient went before a Medical Board. He stated that he now felt perfectly fit except for slight occasional stiffness in his ankle joints. For the last month he had been playing squash and swimming regularly without ill effects.

The Board could find no abnormality now on physical examination and passed him as fit for active service (grade 1), and he returned to the field.

There seems no doubt whatever that this man suffered from a severe attack of diphtheria with peripheral neuritis and myocarditis. This was the final diagnosis written in his Army case notes. There is no record of the administration of antitoxin, and it seems that none was given. This is difficult to understand, but there was considerable delay in getting bacteriologic confirmation of the presence of *C. diphtheriae,* and the infection was regarded initially as a streptococcal one.

Electrocardiographic Reports: According to the patient's records, four electrocardiograms were taken during his illness. Of these, only two actual tracings have been preserved. Only the three limbs were recorded. (It must be remembered that at this time chest leads were not usually taken.) None of the reports, except possibly one, was by an experienced cardiologist. The reports were as follows:

March 12, 1942: Very low voltage T_1, negative T_2, and T_3 iso-electric (figure 1).

April 17, 1942: Rate, 97. Sinus arrhythmia. Right axis deviation. P-R, 0.7 second. Inverted T_1 and T_2. Low voltage. Definite myocardial involvement.

April 29, 1942: Inverted T_1, T_2. Inverted QRS_1 and low voltage throughout. Suggests considerable myocardial damage. No electrocardiographic evidence of significant improvement. (This report was by a medical specialist in No. 5 South African General Hospital.)

May 28, 1952: Inverted T_1; iso-electric T_2 (figure 2). A definitely abnormal tracing.

Subsequent History: This man returned to active duty and fought in the Italian campaign.

On September 12, 1944, he developed infective hepatitis and was treated at a Field Ambulance for one week and then admitted to the Third New Zealand General Hospital. He was jaundiced and his liver was enlarged, and he appears to have been a case of average severity. In his case notes his heart is described as normal.

The patient was discharged on November 5, 1944, and returned to duty. On January 4, 1945, he was admitted with mild concussion and multiple contusions and was discharged after one week.

On March 16, 1945, he embarked at Suez for return to New Zealand, and reached Auckland on April 23, 1945.

He then went on leave, and on May 3, 1945, presented himself before a Medical Board for a routine examination before discharge to civilian life.

The Board found that he had a deviated nasal septum and decided that he should be admitted to the Auckland Hospital for a submucous resection. They also noted that, although his heart appeared to be of normal size and the heart sounds to be normal, many extrasystoles were present. Because of his history of diphtheritic myocarditis, an electrocardiogram was advised.

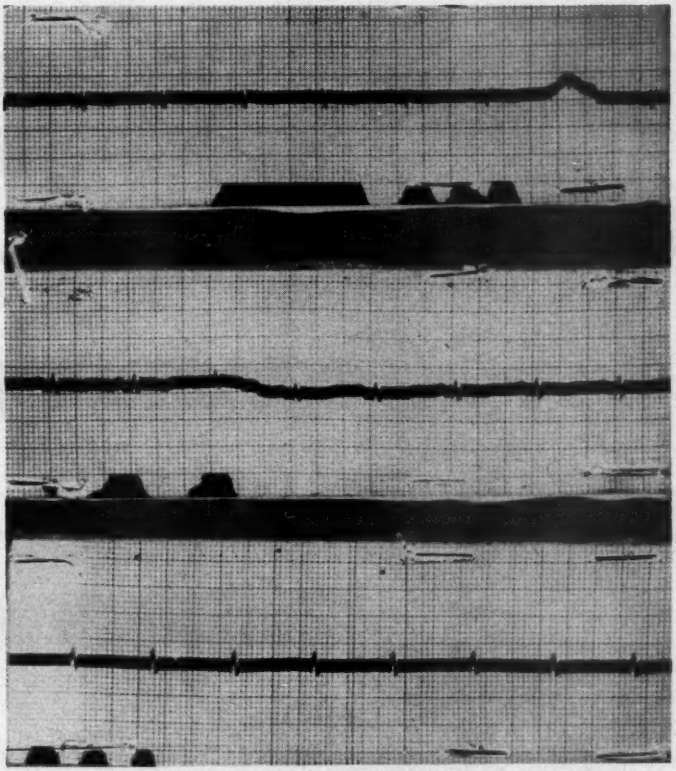

FIG. 1. Electrocardiogram taken on March 12, 1942, when myocarditis was first diagnosed clinically.

The patient was admitted to the Auckland Hospital on June 8, 1945, for his nasal operation, and was discharged on June 14, 1945.

On examination in hospital his heart was not found to be enlarged clinically or radiologically, and was regarded as clinically normal. However, an electrocardiogram taken on June 8, 1945 (figure 3) showed frequent ventricular premature contractions and evidence of myocardial damage. In general, the electrocardiogram was very similar to that taken on May 28, 1942, during his illness in Egypt.

On June 21, 1945, he again appeared before a Medical Board. Again frequent extrasystoles were noted, but otherwise his heart was considered to be normal on physical examination. The Board noted that he said that he felt fit, and that he was

already playing cricket and other sports without any shortness of breath or other complaints. Although the electrocardiogram was recognized as abnormal, the Board apparently did not consider that he had any serious cardiac damage.

The patient, however, was not satisfied with this opinion, because he had been told that his electrocardiogram was abnormal. On September 22, 1945, he was examined by a physician who reported that the patient said he felt well and had no

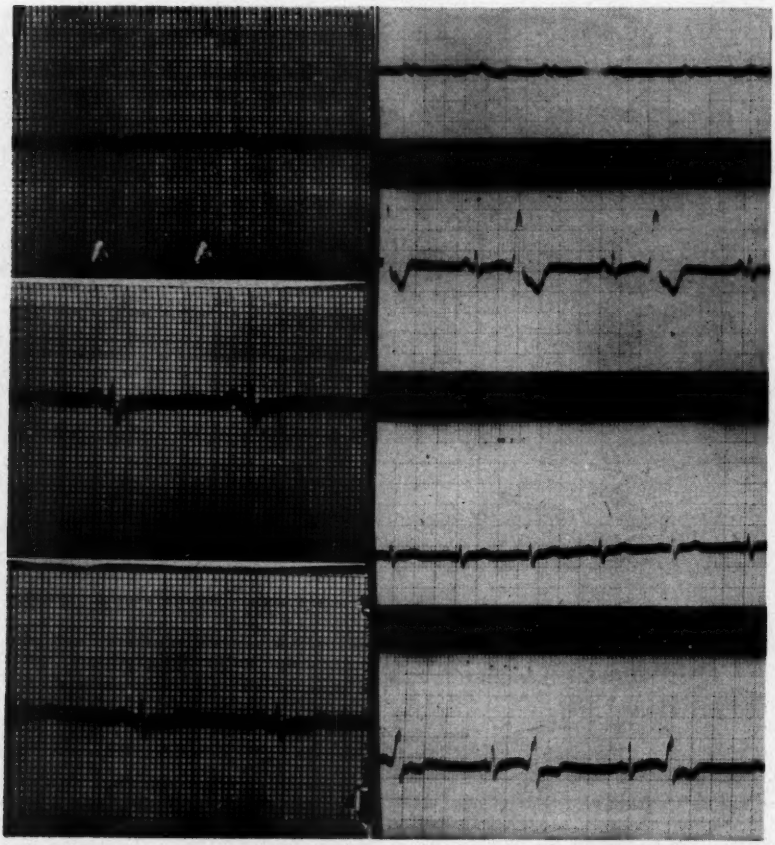

FIG. 2. (*left*) Electrocardiogram taken on May 28, 1942.
FIG. 3. (*right*) Electrocardiogram taken on June 8, 1945.

symptoms and, in particular, that his capacity for exertion was good. He regarded his heart as normal clinically, but made the following report on his electrocardiogram: "Rate 75. PR interval 0.12 sec. R_1 1 mm., R_2 4 mm., R_3 3 mm., R_4 2 mm. Flattened T_1, T_2, T_3, T_4. Splintering S_2, S_3. "The E.C.G. indicates myocardial damage. There is no clinical evidence of myocardial damage but there is electrocardiographic evidence. He should be kept on a small pension and reviewed again in 12 months. *Diagnosis:* Myocardial damage following diphtheria."

On October 1, 1946, the patient was seen again by the same physician. At this time the patient said he was very well, had excellent exercise tolerance and played vigorous badminton. No abnormality was found on physical examination, and it was concluded that there was no remaining disability and his pension was canceled.

This led to further protests from the patient, who was then sent to another physician for examination and was seen on December 21, 1946.

This physician noted that the patient was very fit and engaged in strenuous athletic pastimes and played first-class cricket. The only complaint made by the

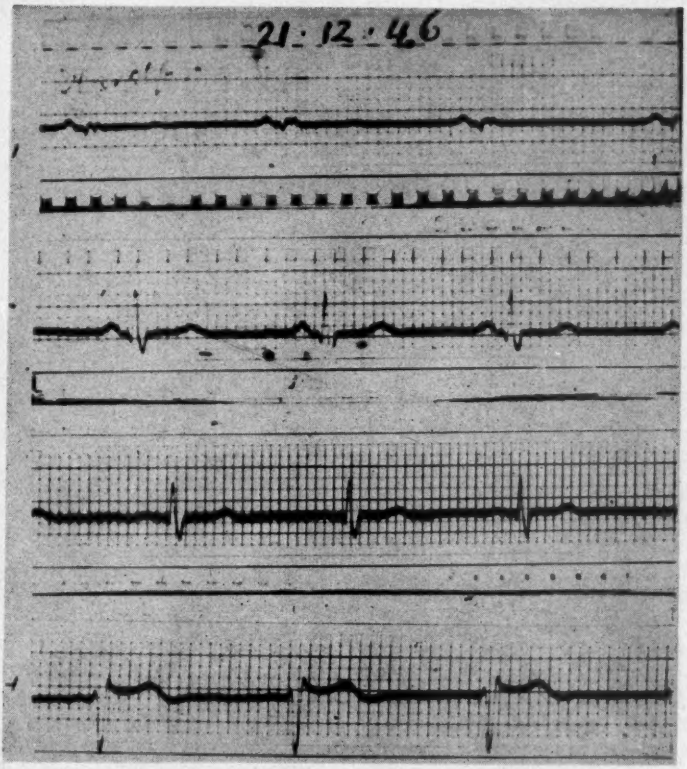

FIG. 4. Electrocardiogram taken on December 21, 1946.

patient was that he thought he tired rather more easily than previously. His heart was found to be normal on physical examination, but again his electrocardiogram was abnormal (figure 4).

The opinion given was that he had no pensionable disability at that time but that deterioration in the future was possible, and it was suggested that he should be informed officially that, if any real disability developed in the future, his pension would be restored. This advice was not acted upon.

From 1946 to 1954 this man was in good health, retained his enthusiasm for sport, and played cricket and badminton. His fellow sportsmen tell me that they

always regarded him as very fit. He did not undergo any further medical examinations.

This patient was first seen by me on September 15, 1954. About eight weeks previously he had felt very tired and listless, and had lacked his normal enthusiasm for his work. Soon after he noticed breathlessness on hurrying or going up a hill, and on two occasions he had what he described as "blackouts." , The first occurred

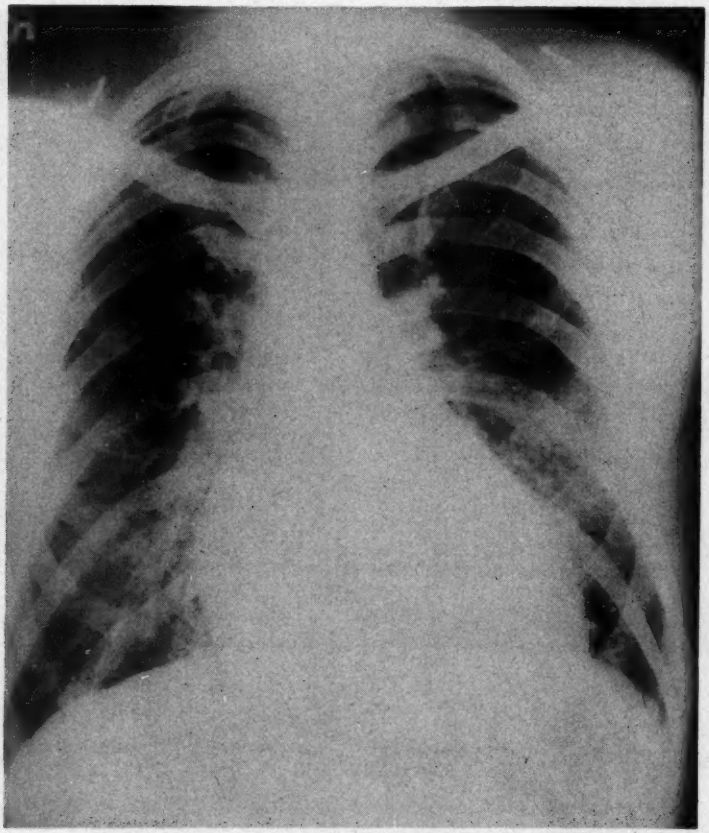

FIG. 5. X-ray of heart on December 2, 1954, showing gross enlargement and pulmonary congestion.

when he was pushing a perambulator in rather a hurry, and the second when pushing a lawnmower. On neither occasion did he lose consciousness, but he felt faint and dizzy.

Four weeks before he was seen he had a febrile illness with a sore throat which lasted for a few days, and after this his condition further deteriorated. He noticed that after a large meal or when walking he developed a tight feeling across the epigastrium and lower chest anteriorly, as if his "chest and stomach were full of wind." He also lost his appetite.

He was admitted to the Auckland Hospital in congestive failure.

On examination the jugular veins were engorged. The apex beat was in the fifth space, six inches from the midsternal line. There were a grade II to III mitral systolic murmur and frequent premature contractions; the blood pressure was 115/80 mm. of Hg. There were râles at both lung bases; the liver edge was just palpable and was tender.

X-rays and screening of his heart showed considerable cardiac enlargement, the cardiothoracic index being 54.3. There was engorgement of the pulmonary vessels. The left ventricle was considerably enlarged, but there was also enlargement of the right ventricle and of the left auricle (figure 5). The electrocardiogram (figure 6) was interpreted as probably indicative of a previous anterior infarction. Although a history of previous diphtheritic infection was obtained, no earlier records were available at this time, and it was not thought that there could be any relationship between his wartime illness and his present condition.

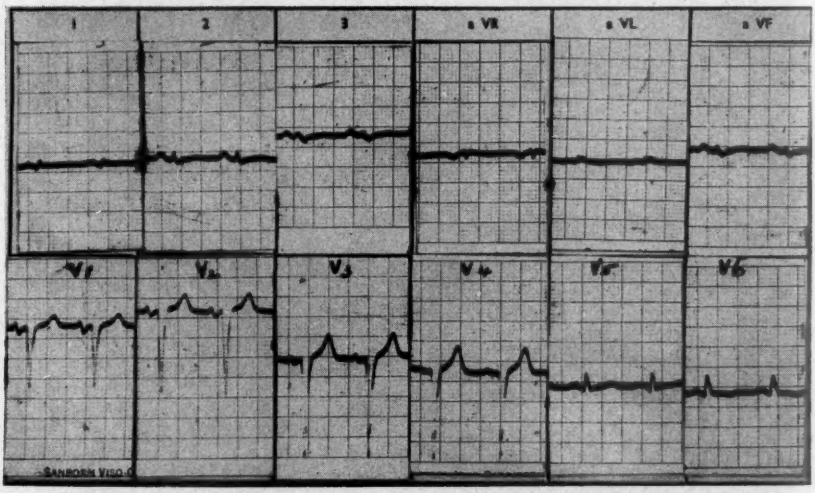

FIG. 6. Electrocardiogram taken on September 16, 1954.

Other investigations were negative. His blood count was normal, his erythrocyte sedimentation rate was 3 mm. in one hour (Westergren), his Wassermann reaction and Laughlen tests were negative, his non-protein nitrogen was 22 mg. per 100 ml., and his blood cholesterol was 170 mg. per 100 ml. Urinalysis was normal.

On Digoxin and bed-rest he rapidly improved, and all signs of failure disappeared. He was discharged on October 2, 1954, after 18 days in hospital, and was instructed to continue on a maintenance dose of digitalis.

He remained fairly well until October 22, 1954, when he again went into congestive failure and was re-admitted to the Auckland Hospital.

His condition was very similar to that on his previous admission, but he now had a protodiastolic gallop, and x-ray of his chest showed further cardiac enlargement. As on previous occasions, he had very frequent extrasystoles.

His digitalis was continued, and he was also given mersalyl and a low sodium diet. He did not improve as on the previous occasion.

He developed a cough with blood-stained sputum, and became pale and anxious and dyspneic, with chest pain and some sacral and ankle edema. A coarse pleural

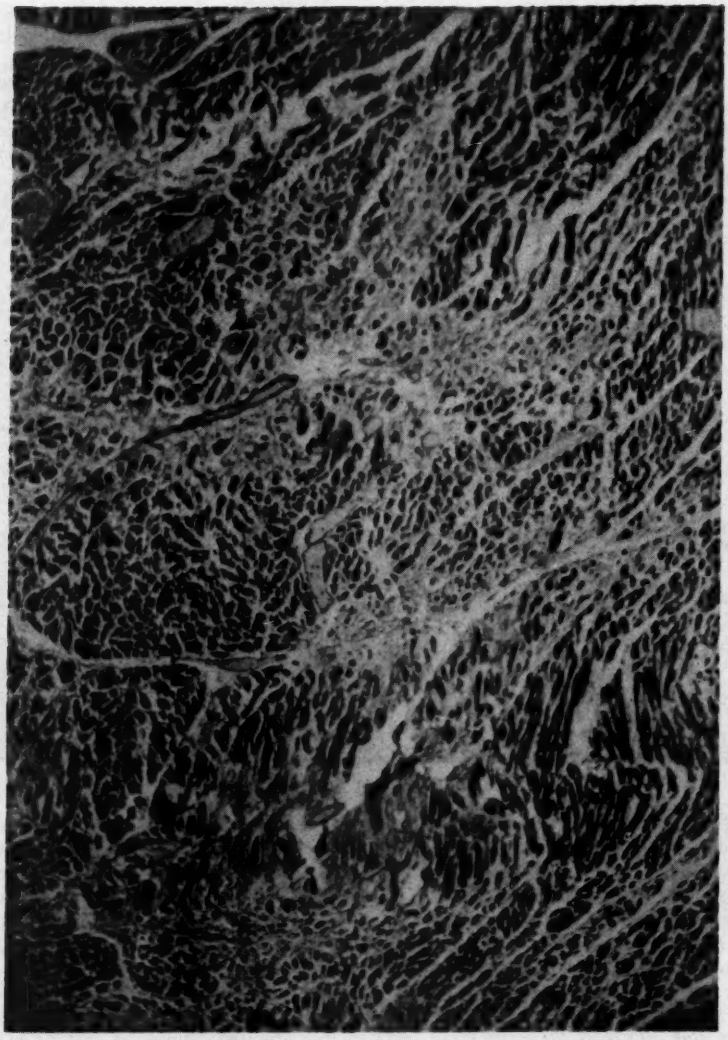

FIG. 7. Section from posterior wall of base of left ventricle, showing diffuse fibrosis in the cardiac muscle. H&E × 175

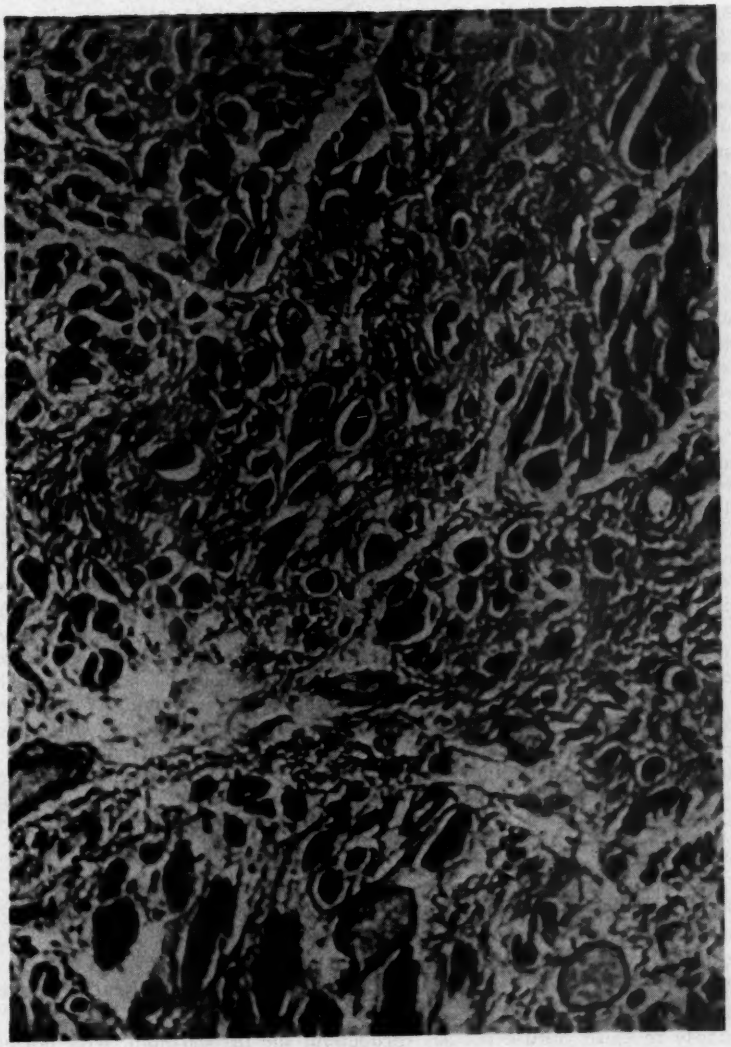

FIG. 8. Higher magnification of previous view, showing fibrous tissue replacing muscle fibers. H&E × 625

rub developed at the left base. There was complaint of pain in the left calf and some deep tenderness, but no other sign of deep vein thrombosis.

He was thought to have pulmonary infarction, and this was confirmed by radiography. He was put on anticoagulants on December 22, 1954. However, his condition deteriorated rapidly and he died suddenly on December 24, 1954.

Summary of Postmortem Findings: Cardiovascular System: The pericardial cavity contained about 40 ml. of clear yellow fluid. The heart was considerably enlarged, weighing 610 gm. The chambers of both ventricles were enlarged, and there was slight hypertrophy of the muscle of both ventricles. The muscle was soft and rather toneless to feel. No naked-eye areas of fibrosis were seen when the myocardium was sliced. The valves appeared to be normal. The coronary arteries were widely patent. The aorta was smooth. *Histologic Examination:* Many sections from both the right and the left ventricles were examined. Sections from the apex and the anterior and posterior walls of the base of the right ventricle showed a diffuse fibrosis. Fine strands of fibrous tissue lay between the muscle fibers. The muscle fibers near the fibrous tissue showed some variation in size, and in parts became splayed out by the fibrous tissue.

Sections from the apex and the anterior and posterior walls of the base of the left ventricle also showed a diffuse fibrosis, with larger and slightly denser areas than those seen in the right ventricle. In places the fibrous tissue formed wavy fibrillae. It could be seen compressing and in parts replacing the cardiac muscle. This fibrous tissue was far in excess of the normal connective tissue of the myocardium, and a large amount of it was quite unrelated to the blood vascular system. It showed up very well in sections stained by van Gieson's method. In none of the sections examined were any inflammatory changes noted, and nothing resembling an Aschoff body was seen. The blood vessels of the myocardium were normal (figures 7 and 8).

Respiratory System: The trachea and main bronchi contained mucopurulent exudate. Both lungs were congested and edematous, and showed several areas of infarction. There were two large areas of infarction in the right lower lobe. An infarct was also present in the right middle lobe. In the posterior part of the left lower lobe there were two small areas of infarction. Elsewhere there were edema fluid and many heart failure cells. The source of the emboli was not found. The pelvic and femoral veins did not contain any thrombi. *Histologic Examination:* Sections from the infarcted areas showed several vessels containing thrombi which were undergoing organization. Some of the infarcts also showed fibroblastic cells.

Alimentary System: The liver was enlarged and the cut surface had a "nutmeg" appearance. *Histologic Examination:* There were congestion of central veins and necrosis of centrilobular cells.

Summary

The history is reported of a patient who suffered from a severe attack of diphtheria with myocarditis and peripheral neuritis in Egypt in 1942.

He died in congestive heart failure in December, 1954.

From the time of his first illness until his death he had permanent electrocardiographic abnormalities.

Autopsy revealed diffuse fibrosis throughout the myocardium, with normal coronary vessels. It is suggested that the fibrosis was a sequel to his diphtheria.

Summario in Interlingua

Ben que acute myocarditis es un communissime complication de diphtheria e es responsabile pro inter 50 e 60% del mortes in iste morbo, le scrutinio del litteratura

pare indicar que damno permanente es un resultato infrequente. Es presentate un breve revista del litteratura relative a iste thema.

Le caso reportate in iste articulo concerne un soldato de Nove Zelanda qui suffreva un sever attacco de diphtheria in Egypto in 1942. Ille suffreva severmente de associate myocarditis e neuritis peripheric, e duo frottis nasal esseva positive pro *Corynebacterium diphtheriae*. Un electrocardiogramma obtenite durante le morbo monstrava signos grossier de un affection myocardial. Post un curso prolongate de morbiditate le patiente se restabliva e retornava al active servicio militar. Ille participava in le integre campania in Italia. Post su dimission ab le armea in 1945, le electrocardiogramma esseva ancora anormal. Illo esseva anormal etiam in 1946.

Le stato de sanitate del patiente remaneva bon, e le patiente habeva un bon tolerantia de exercitio usque 1954, quando ille se presentava con un corde allargate, in stato de sever insufficientia congestive. Ille moriva in decembre 1954. Le autopsia monstrava diffuse fibrose in omne partes de ambe ventriculos sed nulle signo de morbo coronari.

Es formulate le these que isto esseva probabilemente le resultato del myocarditis original que habeva essite causate per diphtheria.

BIBLIOGRAPHY

1. Thompson, W. P., Golden, S. E., and White, P. D.: The heart fifteen to twenty years after severe diphtheria, Am. Heart J. **13**: 534, 1937.
2. Friedberg, C. K.: Diseases of the heart, 2nd Ed., 1956, W. B. Saunders Company, Philadelphia, p. 908.
3. Wood, P.: Diseases of the heart and circulation, 1950, J. B. Lippincott Company, Philadelphia, p. 312.
4. Griffith, G. C., and Herman, L. M.: Persistent complete heart block in diphtheritic myocarditis, J. A. M. A. **148**: 279–282, 1952.
5. Hoel, J., and Berg, A. H.: Persistent diphtheritic heart disorders, Acta med. Scandinav. **145**: 393–405, 1953.

DISSEMINATED COCCIDIOIDOMYCOSIS DEMONSTRATED BY NEEDLE BIOPSY OF THE LIVER*

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Granulomata in the liver have been previously demonstrated in tissue obtained by needle biopsy in such diseases as tuberculosis,[1–8] sarcoidosis,[2, 3, 9–14] Hodgkin's disease,[3] lymphopathia venereum,[3] tularemia, [2, 3, 15] brucellosis,[2, 3, 16, 17] syphilis,[2, 3] leprosy, [18] and fungus infections.[14]

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When involvement of the liver occurs in these diffuse granulomatous diseases, the foci are usually widely scattered.[5, 14, 16] Zamcheck and Sidman [19] have reviewed various studies which indicate the validity of the liver biopsy specimen as a representative histologic sample in such conditions, and in summary state that needle biopsy accurately samples all diffuse anatomic lesions and the majority of focal lesions. There is good correlation between needle biopsy specimens and autopsy findings on patients having focal lesions in the liver.[20-24] In granulomatous or any focal disease in the liver, the finding of a positive specimen is significant. A normal specimen excludes the presence of a diffuse but not of a focal disease of the liver.

In a review of 95 cases of disseminated coccidioidomycosis, Forbus [25] records only one patient in whom enlargement of the liver was noted, although 50 of these patients died of their disease and were autopsied. Of those patients autopsied, 17 had grossly abnormal livers, but 30 showed microscopic evidence of scattered specific lesions of *Coccidioides immitis*. Thus, coccidioidomycosis disseminated to the liver was demonstrated by autopsy, even though these patients had had no abnormal physical signs pointing to hepatic involvement. It is of interest in this series of autopsy cases that only two other visceral organs were found to be more often involved—the lungs in 43 patients and the spleen in 35.

It is the purpose of this paper to report a case of disseminated coccidioidomycosis in which liver biopsy successfully demonstrated the etiology of the disease, and to point to the value of liver biopsy in the differential diagnosis of this disease, whether hepatomegaly is present or not. A therapeutic trial with chloroquine diphosphate will be mentioned.

Case Report

A 24 year old white veteran was admitted to the William Beaumont Army Hospital, Fort Bliss, Texas, on January 16, 1956. He complained of having had a recurrent fever of 101° to 103° F. each evening since the middle of December, 1955, occasionally associated with night sweats and shaking chills. He had also noted a 15 pound weight loss, generalized weakness, exertional dyspnea and nervousness. There were no other complaints.

The patient had been born and raised in the El Paso area and, except for the usual childhood diseases and mild seasonal hay fever every August, he had enjoyed excellent health and strength. There were no other symptoms suggestive of allergy. He had served four consecutive years prior to 1955 in the Air Force in the southwestern United States, mainly in Arizona and Texas. Since then he had resided in El Paso, where he was employed as a travel agent.

Physical examination revealed a well developed and well nourished young man who appeared moderately and chronically ill. His temperature was 100° F.; pulse, 80; respirations, 16 per minute. He was 5 feet 7 inches tall and weighed 153 pounds. His conjunctivae were slightly congested. Physical examination was otherwise normal.

Ten days prior to admission to the hospital this patient had had a total leukocyte count of 19,900 cells per cubic millimeter, with a differential count of 16% polymorphonuclear leukocytes, 16% lymphocytes, 1% monocytes and 67% eosinophils. At the same time, x-ray examination of the chest had shown mild bilateral peribronchial opacification near the hili of the lungs. On the day of admission to the hospital the patient had had a total leukocyte count of 16,000 cells per cubic millimeter,

with a differential count of 38% neutrophils, 30% lymphocytes, 4% monocytes and 28% eosinophils. The red blood cell count, hemoglobin, hematocrit, platelet count, clotting time, clot retraction and Rumpel-Leede test were normal. The erythrocyte sedimentation rate was 33 mm./hr. Cardiolipin test for syphilis was negative, and urinalysis was normal.

In view of the patient's fever, eosinophilia, leukocytosis and elevated erythrocyte sedimentation rate, laboratory tests were initially directed toward the possibility of an infectious, lymphomatous, allergic or collagen disease. Repeated urinalyses were normal, as were multiple cultures of the urine, blood, nasopharyngeal secretions and stools. No ova or parasites were seen in repeated stool examinations. The heterophil antibody titer and the serum agglutination tests for brucellosis, typhoid and paratyphoid fever were within normal limits. Thick blood smears showed no plasmodia. Skin tests with purified protein derivative for tuberculosis were negative in the first and second dilutions, as were skin tests with trichinella antigen, Frei antigen, histoplasmin and freshly prepared coccidioidin in dilutions of 1/1,000 and 1/100. A 12-lead electrocardiogram was normal. Teleroentgenogram of the chest revealed a broadened superior mediastinal shadow, especially on the right, which was thought to be due to peritracheal adenopathy, but the lung fields were clear. A barium swallow with fluoroscopy of the chest further supported this finding. An upper gastrointestinal series was normal. A skeletal survey, including x-ray examination of the skull, spine, pelvis and lower extremities, failed to reveal any abnormality. Aspirated sternal bone marrow prepared with Wright's stain revealed an increased proportion of eosinophils in the marrow. A differential count on this marrow revealed 52% polymorphonuclear leukocytes (15% band forms), 10% myelocyte C forms, 16% mature eosinophils, 9% eosinophilic myelocyte C forms, 1% eosinophilic myelocyte B forms and 12% lymphocytes; 7 normoblasts and 2 late erythroblasts were seen per 100 white blood cells.

There was never any palpable lymphadenopathy, but because of the possibility that the lymph nodes in the right supraclavicular area might be involved in association with the demonstrated mediastinal lymphadenopathy, the right supraclavicular fat pad was deeply excised, but no nodes were found in this specimen. A biopsy of the right anterior scalene muscle revealed normal striated muscle and no evidence of trichinosis or arterial abnormality. The patient's febrile course continued, with normal temperatures in the morning and spiking rises to 101° to 103° F. from 4 to 8 o'clock each evening.

On January 25, 1956, a tender, rounded splenic edge was palpable one fingerbreadth below the left costal margin, and tenderness and slight guarding of the right upper abdominal quadrant were also noted, although hepatomegaly could not be demonstrated. The total serum proteins, A/G ratio, cephalin-cholesterol flocculation, total and direct serum bilirubin, total and esterified cholesterol, plasma prothrombin time and bromsulfalein dye retention tests were all within normal limits and remained so. A thymol turbidity of 10 clinical units (upper limits of normal, 7.5 units) was noted. On February 6, 1956, a tender, smooth and rounded liver edge was felt one fingerbreadth below the right costal margin, and the liver gradually enlarged until its edge could be felt two to three fingerbreadths below the right costal margin 10 days later. On February 8, 1956, a repeat x-ray examination of the chest revealed no change from that previously noted. The intermittent fever, leukocytosis and eosinophilia continued.

On February 16, 1956, a transthoracic needle biopsy of the liver, using the Vim-Silverman needle, was accomplished without untoward results and yielded a cylinder of hepatic tissue measuring approximately 2 cm. in length and 1 mm. in diameter. This specimen was light brown in color, and many scattered, pinpoint, translucent foci were seen grossly. Microscopic examination of this specimen, after staining by

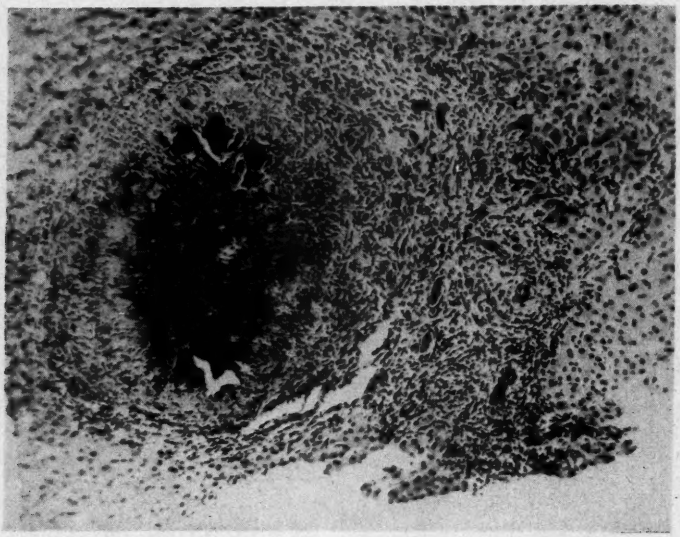

FIG. 1. One of multiple granulomata in liver biopsy specimen. × 50. (H&E.)

the hematoxylin-eosin method, revealed scattered granulomata characterized by multinucleated giant cells, epithelioid cells and leukocytes, the majority of which were eosinophils. Many lymphocytes were also seen (figure 1). Most of the granulomata had fairly compact looking centers, and only one showed a necrotic center. The necrosis was not of the caseation type but was stippled with hema-

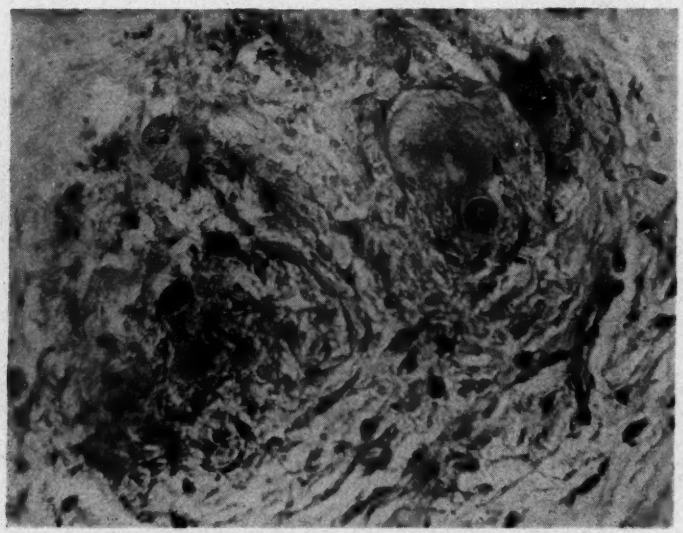

FIG. 2. Two spherules of *C. immitis* in liver biopsy specimen. × 300. (Periodic acid-Schiff stain.)

toxylin-stained material resembling degenerating nuclei, and eosinophilic material which resembled the granules of eosinophils. There was a sprinkling of eosinophils on the peripheries of the granulomata and throughout the hepatic sinuses, and clusters of eosinophils were seen at random throughout the liver cords. Minimal fatty metamorphosis was seen. Special stains showed no acid-fast bacilli. Periodic acid-Schiff stains demonstrated Schiff-positive spherules in one of the granulomata. These spherules showed no evidence of budding, and had doubly refractile walls which contained amorphous material, and appeared to be *Coccidioides immitis* (figure 2). The slides were examined by the Armed Forces Institute of Pathology, which concurred in the diagnosis of coccidioidomycosis of the liver.

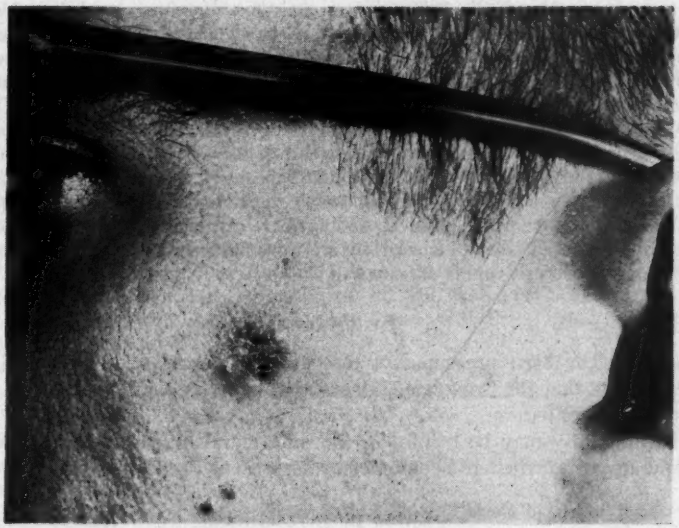

FIG. 3. Photograph of skin lesion described in text.

On February 21, 1956, complement fixation tests were drawn which were reported as follows: histoplasmosis, negative; blastomycosis, positive in a dilution of 1/4; coccidioidomycosis, positive in a dilution of 1/256. A colloidal agglutination test for histoplasmosis was negative.

The patient's febrile course, eosinophilia and hepatosplenomegaly continued as noted above. He was kept on a high calorie diet and bed-rest. By the last week in February his weight had reached its lowest level (139 pounds), and a slightly raised, cornified, violaceous skin lesion appeared on the left malar eminence (figure 3). This lesion gradually enlarged during the next week to a diameter of 1 cm., and showed no evidence of drainage or healing. On February 28, 1956, the white blood cell count was 9,100 per cubic millimeter, with a differential count of 76% neutrophils, 18% lymphocytes, 3% monocytes and 3% eosinophils. The erythrocyte sedimentation rate was 45 mm./hr. There was no evidence of anemia.

Beginning on February 29, 1956, the patient received an initial dose of chloroquine diphosphate, 1 gm. by mouth, followed in eight hours by 0.5 gm. by mouth. Since that time he has received 0.25 gm. of chloroquine disphosphate by mouth twice daily, and while receiving this drug for the past 72 days has shown no further temperature elevation or symptoms except for slight fever and coryza associated with

a mild upper respiratory infection of several days' duration. He has had a weight gain to 145 pounds. On March 3, 1956, the white blood cell count was 5,100 per cubic millimeter, with 45% neutrophils, 35% lymphocytes, 1% monocytes and 19% eosinophils. On March 19, 1956, the complement fixation tests were negative in all dilutions for histoplasmosis and blastomycosis, and positive in a 1/128 dilution for coccidioidomycosis. The alkaline phosphatase, cephalin-cholesterol flocculation, thymol turbidity, bromsulphalein dye retention, total and direct bilirubin and total serum proteins and A/G ratio were normal. On April 13, 1956, his leukocytes numbered 7,000 per cubic millimeter, and the differential white blood cell count was normal and has remained within normal limits since.

The skin lesion previously mentioned decreased slowly in size but did not heal. It was excised on March 22, 1956. Microscopic examination revealed a thickened hyperkeratotic epidermis, broad rete pegs, and evidence of an acute and chronic inflammatory infiltration consisting of polymorphonuclear leukocytes, as well as lymphocytes, plasma cells and polymorphonuclear eosinophils. Hematoxylin-eosin, periodic acid-Schiff and acid-fast stains failed to reveal a causative agent. The site of the lesion healed, with considerable scarring thereafter. The patient's liver gradually decreased in size and was no longer palpable by March 30, 1956, and the spleen could no longer be felt after April 10, 1956.

The patient is presently (May 10, 1956) asymptomatic and afebrile, gaining weight and has no abnormal physical findings. X-ray examination reveals definite decrease in the size of the broadened superior mediastinum, and his total and differential white blood cell counts are normal.

Summary

1. A case has been presented of disseminated coccidioidomycosis with the unusual feature that the organism, *Coccidioides immitis,* was revealed by needle biopsy of the liver.

2. Liver biopsy may be helpful in the differential diagnosis of disseminated coccidioidomycosis, whether hepatomegaly is present or not.

Summario in Interlingua

Es reportate un caso de coccidioidomycosis disseminate in un masculo de juvene etate. Le etiologia del morbo esseva demonstrate in un specimen de biopsia hepatic obtenite per medio del agulia de Vim-Silverman e colorate per le methodo Schiff a acido periodic. Multiple granulomas hepatic e le organismo *Coccidioides immitis* esseva vidite. Le autores signala le valor del biopsia hepatic in le diagnose differential de iste morbo, si o non hepatomegalia es presente.

BIBLIOGRAPHY

1. Ward, J. R., Ulevitch, H., and Schiff, L.: The diagnostic value of needle biopsy of the liver, Gastroenterology **28**: 34, 1955.
2. Schiff, L.: The clinical value of needle biopsy of the liver, Ann. Int. Med. **34**: 948, 1951.
3. Wagoner, G. P., Anton, A. T., Gall, E. A., and Schiff, L.: Needle biopsy of the liver. VIII. Experiences with hepatic granulomas, Gastroenterology **25**: 487, 1953.
4. Rumball, J. M.: Needle biopsy of the liver, Am. J. Surg. **131**: 140, 1952.
5. Cohen, A. G., and Giges, B.: Punch biopsy of the liver in detection of hematogenous tuberculosis, J. A. M. A. **146**: 1416, 1951.
6. McHardy, G., Browne, D. C., and Edwards, E.: Peritoneoscopic and biopsy evaluation of hepatic disease, Gastroenterology **9**: 682, 1947.
7. Craddock, C. G., and Meridith, H. C., Jr.: Punch liver biopsy in diagnosis of miliary tuberculosis, report of case, New England J. Med. **241**: 527, 1949.

8. Rumball, J. M., and Baum, G. L.: Liver biopsy culture in diagnosis of miliary tuberculosis: case report, Gastroenterology **22**: 124, 1952.
9. Volwiler, W., and Jones, C. M.: Diagnostic and therapeutic value of liver biopsies, with particular reference to trochar biopsy, New England J. Med. **237**: 651, 1947.
10. Baird, M. M., Boyoch, A., and Fenwick, J. B.: Liver biopsy in sarcoidosis, Canad. M. A. J. **62**: 563, 1950.
11. Scadding, J. G., and Sherlock, S.: Liver biopsy in sarcoidosis, Thorax **3**: 79, 1948.
12. Shay, H., Berk, J. E., Sones, M., Aegerter, E. E., Weston, J. K., and Adams, A. B.: The liver in sarcoidosis, Gastroenterology **19**: 441, 1951.
13. Van Beek, C., and Haex, A. J. C.: Aspiration-biopsy of liver in mononucleosis infectiosa and in Besnier-Boeck-Schaumann's disease, Acta med. Scandinav. **113**: 125, 1943.
14. Klatskin, G., and Yesner, R.: Hepatic manifestations of sarcoidosis and other granulomatous diseases: study based on histological examination of tissue obtained by needle biopsy of liver, Yale J. Biol. and Med. **23**: 207, 1950.
15. Bernstein, A.: Tularemia: report of 3 fatal cases with autopsies, Arch. Int. Med. **56**: 1117, 1935.
16. Spink, W. W., Hoffbauer, F. W., Walker, W. W., and Green, R. A.: Histopathology of liver in human brucellosis, J. Lab. and Clin. Med. **34**: 40, 1949.
17. Cazal, P.: Les lesions de l'hepatite brucellienne, Semaine d. hôp. Paris **25**: 1351, 1949.
18. Hurley, T. H.: Liver biopsy: some observations on its value in diagnoses, M. J. Australia **1**: 747, 1952.
19. Zamcheck, N., and Sidman, R. L.: Needle biopsy of the liver. I. Its use in clinical-investigative medicine, New England J. Med. **249**: 1020, 1953.
20. Wagoner, G. P., Ulevitch, H., Abernathy, E. L., Gall, E. A., and Schiff, L.: Correlation of results of needle biopsy of the liver with autopsy findings, J. Lab. and Clin. Med. **36**: 1000, 1950.
21. Giesen, C. P., Koepsell, J. E., Hastings, E. V., and Lindert, M. C. F.: Correlation of punch liver biopsy with autopsy material, Am. J. Digest. Dis. **18**: 304, 1951.
22. Molle, W. E., and Kaplan, L.: Needle biopsy of liver: general considerations, California Med. **76**: 16, 1952.
23. Bowden, L., and Kravitz, S.: Needle biopsy of the liver: a diagnostic aid in the treatment of cancer, Cancer **6**: 1010, 1953.
24. Ward, J. R., Schiff, L., Young, P., and Gall, E. A.: Needle biopsy of the liver. IX. Further experiences with malignant neoplasm, Gastroenterology **27**: 300, 1954.
25. Forbus, W. D.: A study of 95 cases of the disseminated coccidioidomycosis with special reference to the pathogenesis of the disease, Mil. Surgeon **99**: 653, 1946.

PRIMARY HYPERPARATHYROIDISM ASSOCIATED WITH PEPTIC ULCER: A REPORT OF TWO CASES*

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Introduction

Recently two patients with primary hyperparathyroidism have been observed whose clinical manifestations were such that in both instances there was

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considerable delay in arriving at the correct diagnosis. In these two patients the clinical picture was that of peptic ulcer associated with gastroenteric symptoms of 20 years' duration. Because of these symptoms both patients underwent gastric resections before the hyperparathyroidism was recognized and corrected. It would appear warranted to report these two patients because the usual clinical manifestations related to skeletal and/or renal involvement associated with hyperparathyroidism were absent or were minor problems. A review of the literature shows that gastroenteric symptoms are a common major manifestation of primary hyperparathyroidism. However, the association of peptic ulcer with hyperparathyroidism is less appreciated.

Case Reports

Case 1. A 37 year old Negro housewife was admitted to the Cincinnati General Hospital April 18, 1955. Her chief complaints were nausea and vomiting, which had been present during much of her adult life but had become intolerable during the preceding two weeks. At the age of 17 the patient had received medical treatment at the Cincinnati General Hospital for a duodenal ulcer accompanied by melena. The patient had taken calcium carbonate powder intermittently and had consumed one quart of milk daily for the next 20 years. In 1952 the patient was admitted to another hospital because of epigastric pain, nausea and vomiting. She was treated with gastric suction and parenteral fluids. She refused the recommendation of an abdominal operation and was discharged after six weeks of hospitalization. In January, 1955, the patient was admitted to the Cincinnati General Hospital and a diagnosis of pyloric obstruction was made. For several weeks prior to that admission she had experienced persistent vomiting. In January, 1955, an upper gastrointestinal series showed a marked cloverleaf deformity of the duodenal bulb, with what was thought to be an active ulcer niche. In February, 1955, the patient underwent a Billroth I subtotal gastrectomy, which was followed by an uneventful postoperative course. At the time of discharge from the hospital, in February, 1955, the patient weighed 93 pounds. Shortly thereafter she again experienced nausea, noted occasional episodes of dizziness, and began to vomit recently ingested food. During the two weeks prior to her admission on April 18, 1955, the patient had vomited persistently and had been unable to retain liquid or solid foods. She lost 15 pounds between February and April, 1955. Additional complaints were severe constipation, polyuria and polydipsia. There had been no hematemesis or recent melena. The patient also gave a history of rickets in early childhood which had resulted in bowing deformities of her legs.

Physical Examination: The temperature, pulse and respiration were normal, and the blood pressure was 130/86 mm. Hg. The patient weighed 78 pounds and appeared to be chronically ill, malnourished, weak and mildly dehydrated. She exhibited a bizarre affect and appeared detached from her environment to such an extent that she was considered mentally dull. All other aspects of the examination were completely within normal limits except for rachitic bowing of her lower legs and hyperactive tendon reflexes.

Pertinent Laboratory Data: Hemoglobin, 12 gm.%; white blood count, 6700/mm^3; differential, normal. Urinalysis: albumin, trace; specific gravity, 1.002, changing to 1.010 after 16 hours of water deprivation; microscopic, normal. Blood urea nitrogen, 4.5 mg.%. Serum: CO_2, 27 mEq./L.; sodium, 140 mEq./L.; chloride, 104 mEq./L.; potassium, 1.7 mEq./L., changing to 4.2 mEq./L. after nine days of a regular diet plus 42 gm. of potassium chloride. A serum potassium concentration obtained shortly before discharge was 2.7 mEq./L. Serum alkaline phosphatase,

4.2 Bodansky units; serum albumin, 4.0; globulin, 2.6 gm.%. Electrocardiogram, normal. The calcium and phosphorus data are shown in table 1.

Course: During the first several days in the hospital the patient received parenteral fluids while the possibility of upper gastrointestinal obstruction was being considered. The finding of a persistently low serum potassium concentration resulted in a search for other electrolyte abnormalities. Because the hypokalemia was unaccompanied by any evidence of hyporeflexia or electrocardiographic changes, studies were made of other serum electrolytes. It was at this time that the findings of hypercalcemia and hypophosphatemia first suggested the diagnosis of hyperparathyroidism. X-ray studies confirming the diagnosis demonstrated the absence of

TABLE 1

Date	Serum mg. %		Urine mg./day	
	Calcium	Phosphorus	Calcium	Phosphorus
		Case 1		
4-27-55	16.4	2.4		
5-11-55	16.9	1.5	292	262
5-18-55	18.0	1.2	189	
5-19-56		Excision of Adenoma		
5-21-55	10.0	2.2	137	46.6
5-24-55	10.4	1.8	77	6.2
6-22-55	9.6	2.4		
		Case 2		
12-15-55	14.6	1.5	226	372
1- 5-56	11.2	1.1	180	305
1- 9-56	11.5	1.0	132	250
1-17-56	11.6	2.4	118	
1-17-56		Excision of Adenoma		
1-18-56	8.6	3.0	120	39
1-21-56	8.9	2.4	32	
1-24-56	9.0	2.8	27	
2- 2-56	8.6	3.1	54	

Both patients were on a daily intake of 200 mg. of calcium during the periods noted above before excision of the adenomas.

lamina dura, with otherwise normal bones and a displacement of the barium-filled esophagus to the right at a level in the region of the parathyroids. On May 19, 1955, a large parathyroid adenoma was removed from the area noted on barium swallow. Following the operation the patient improved dramatically, and she has since been free of symptoms. She has gained approximately 25 pounds in weight, is quite alert, and at present attends an evening business school. The results of the preoperative and postoperative calcium and phosphorus studies are listed in table 1.

The report of the pathologist was as follows. "Gross description: The specimen consists of a thinly encapsulated mass measuring 4 x 3 x 3 cm. and weighing 6.5 gm.: on section it is found to be soft and cut surface exhibits a homogeneous, yellowish-pink appearance: minute foci of punctate hemorrhage are encountered. Microscopic description: The lesion exhibits a diffuse overgrowth of chief cells with uniform character. An interlacing alveolar structure is focally manifest. No mitotic

activity is noted and there is no evidence of neoplasm. Diagnosis: Parathyroid adenoma, chief cell type."

Case 2. A 32 year old housewife was admitted to the Cincinnati General Hospital on December 4, 1955, because of a threatened abortion at the sixth month of pregnancy and because of flank pain. Since the age of 12 she had had abdominal complaints. She first noticed intermittent heartburn, which was relieved by baking soda. This distress was accompanied at times by nausea, vomiting and constipation. In July, 1952, the patient had experienced her first episode of coffee-ground vomitus. In November, 1952, she experienced a perforation of a duodenal ulcer which necessitated surgical closure. In March, 1953, she underwent a cholecystectomy for cholecystitis and cholelithiasis. From March, 1953, until October, 1954, she experienced epigastric burning pain. During this time she occasionally vomited coffee-ground material, and there were short periods during which she noticed tarry stools. Constipation became severe and was presumed to be the result of treatment with Banthine. In October, 1954, because of the persistence of gastrointestinal symptoms, the patient underwent a Billroth I subtotal gastric resection. In March, 1955, she was re-admitted to the hospital because of the postoperative persistence of vomiting and epigastric pain associated with weight loss. There was gastroscopic evidence of a narrowed gastroduodenal stoma, but the abnormality could not be demonstrated on an upper gastrointestinal x-ray examination. In March, 1955, surgical revision of what was considered to be a narrowed gastroduodenal stoma was performed. This produced some amelioration of symptoms. Between September and December, 1955, the patient had experienced periodic weakness which was so severe that on several occasions her husband had to assist her out of bed in the morning. She also had experienced frequent pain in her wrists and knees. She had had five previous normal pregnancies and five normal children. Her sixth pregnancy, in 1953, ended in a miscarriage at six months.

Physical Examination On Admission: The temperature, pulse and respiration were normal, and the blood pressure was 120/70 mm. Hg. The patient was an alert, well developed and well nourished young woman in moderate distress as a result of flank and lower abdominal pain. A soft mass, approximately 3 by 4 cm., was palpated in the region of the left inferior pole of the thyroid. Left flank tenderness was elicited. No other abnormalities were noted. The uterine fundus was enlarged to the umbilicus and the fetus was in breech position. The skeletal and muscular systems were normal to examination.

Pertinent Laboratory Data: Hemoglobin, 10.0 gm.%; white blood count, 11,000; blood urea nitrogen, 5.0 mg.%. Serum: albumin, 2.90 gm.%; globulin, 2.95 gm.%; CO_2, 24.5 mEq./L.; chloride, 107 mEq./L.; sodium, 144 mEq./L.; potassium, 5.0 mEq./L. A serum alkaline phosphatase was 2.4 Bodansky units. Urinalysis: specific gravity, 1.015; albumin, negative; sugar, negative; microscopic, 1 to 3 white blood cells per high power field; culture, negative. Intravenous pyelogram: prompt bilateral excretion of the contrast substance in five minutes; left ureteral calculus located in distal third; right renal calculus located in the renal pelvis. Electrocardiogram: nonspecific T wave changes. The patient's calcium and phosphorus determinations are shown in table 1.

Course: Because of the roentgen findings of a left ureteral calculus and a right renal calculus, calcium and phosphorus determinations were obtained. The abnormalities of the serum content of calcium and phosphorus supported the clinical impression of hyperparathyroidism. These results are recorded in table 1. Within the first few days of hospitalization the patient passed three stones which, on analysis, proved to be calcium carbonate stones. Deviation of the esophagus to the right at the level of the seventh cervical vertebra was demonstrated on a barium esophagram. This was considered to be a constant pressure defect from a soft tissue density noted

to be in this area. The lamina dura were demineralized. X-rays of the skull, long bones and spine were normal.

The patient insisted on leaving the hospital for one week on December 20. She was re-admitted December 27. On December 28 a fetal foot prolapsed and shortly thereafter the patient delivered a 1 pound 4 ounce baby which lived 48 hours. The infant's serum calcium at birth was 14.8 mg.%, the serum phosphorus was 5.8 mg.%, and the serum alkaline phosphatase was 4.0 Bodansky units. The mother's serum calcium concentration at the time of delivery was 11.6 mg.% and her serum phosphorus, 2.4 mg.%. Postpartum hemorrhage occurred and was estimated at 1,000 ml. The patient received one unit of whole blood. Otherwise she had a normal puerperal course.

Surgical exploration of this patient's neck was performed January 17, 1956, at which time a cystic parathyroid adenoma, 3.5 cm. in diameter, was removed. The adenoma was located in the area of the pressure defect demonstrated on the barium esophagram. A sternal biopsy was obtained during surgery. The patient's postoperative course was satisfactory. Her gastroenteric symptoms subsided within several days of the operation. The calcium and phosphorus analyses performed postoperatively are recorded in table 1. Because the calculus in the distal third of the left ureter remained in the same position for approximately two months, a left ureterolithotomy was performed in February, 1956. The patient's course following this procedure was uneventful.

The pathology report of the parathyroid tumor and of a specimen of sternum was as follows: "Gross description: The specimen consists of a thinly encapsulated, cystic mass measuring 3.5 cm. in its greatest diameter. On section turbid, reddish brown fluid is released from the slit-like cystic cavity, the lining of which has a dark gray membranous appearance. The solid component of the lesion measures 1 to 3 cm. and consists of friable, brown substance. Microscopic description: There are innumerable collapsed cystic cavities with serous content. The solid portion of the tumor consists of broad sheets of chief cells with relatively monotonous pattern. Nuclei are for the most part uniform with occasional large symplastic forms. Mitotic figures are absent. Cytoplasm is scanty and clear staining. Cells are often arranged in perithelial manner and occasionally form palisade-like rows along sinusoidal channels. There is no evidence of malignancy. Diagnosis: Parathyroid adenoma, chief cell type, with multiple cyst formation." The sternal biopsy report was as follows: "The section consists of thin cortical bone with a narrow segment of subjacent cancellous marrow. The trabeculae comprising the latter are not remarkable. The marrow substance is active and normal in appearance. Within the cortex itself, however, there is focal lacunar resorption. This is characterized by moderate enlargement of lacunar spaces which contain loose fibrous tissue. The periphery of each space is smooth, although an occasional osteoclast lies contiguous with it. There is no osteoblastic activity manifest. The lesion is not characteristic of osteitis fibrosa cystica, but may be considered consistent with it."

Fetal Pathology: The infant weighed 485 gm. Atelectasis and patches of pneumonia were present in the lungs. Sections of all organs were stained with von Kossa's stain for calcium and no abnormal calcium deposit was found. No definite evidence of hyperparathyroidism was observed on the sections of bone. No parathyroid tissue was detected by gross dissection. There was some disagreement among the pathologists as to whether the fetal bones were normal. No specific diagnosis could be made.

Discussion

These two patients demonstrated the toxic manifestations of hyperparathyroidism attributed to hypercalcemia. These manifestations included anor-

exia, nausea, vomiting, epigastric pain, constipation, weakness, weight loss, polyuria and polydipsia. Albright and his colleagues were among the first to point out this category of patients, namely, those who did not have major bone or stone problems.[1] Similar manifestations of hypercalcemia occur in conditions which impose immobilization of an appreciable portion of the patient, in vitamin D intoxication, and in extensive metastatic bone disease.[2, 3] In 1934 Gutman and his associates described patients with hyperparathyroidism who had symptoms suggesting peptic ulcer, namely, anorexia, nausea, vomiting and epigastric pain, but who did not have peptic ulcers.[4] In 1946 Rogers emphasized the association of actual peptic ulcer and hyperparathyroidism.[5] In a later publication this author and collaborators stated that the coexistence of peptic ulcer with hyperparathyroidism obscured the diagnosis of hyperparathyroidism because the gastroenteric symptoms could be readily ascribed to the ulcer.[6] In the two young women in this report, both duodenal ulcers and associated gastroenteric symptoms were present. In retrospect, it seems likely that the gastric surgery performed on these two patients was actually for relief of symptoms of hypercalcemia and might not have been necessary had the hyperparathyroidism been corrected earlier. This appears to be a reasonable assumption, inasmuch as these two patients continued with their gastroenteric symptoms. Moreover, these symptoms were relieved dramatically in each instance when the parathyroid adenoma was removed.

The finding of duodenal ulcer in both of these patients is consistent with reports indicating that peptic ulcer occurs significantly more frequently in patients with hyperparathyroidism than in the general population.[7, 8, 9, 10] An adequate explanation for this association is lacking. However, Schiffrin demonstrated in dogs that parathyroid hormone could effect an increase in volume, acidity, chloride concentration and pepsin concentration of gastric secretion.[11] The findings on these two patients do not clarify the association of peptic ulcer and hyperparathyroidism, and do not answer the question of whether one condition may have caused the other. The known increased incidence of peptic ulcer in patients with hyperparathyroidism suggests that the latter disease plays a causal role in the genesis of the former. Knowledge of the incidence of hyperparathyroidism in the peptic ulcer population would help to decide this point. Studies are indicated to determine the incidence of hyperparathyroidism in all patients with peptic ulcer, particularly in those whose ulcer symptoms are not responding satisfactorily to treatment. It has been suggested that the administration of milk and alkali for the treatment of an ulcer to a patient with hyperparathyroidism and peptic ulcer can accentuate the patient's gastroenteric symptoms and further impair renal function.[6]

There are two features of these patients which deserve comment, even though they are unrelated to the gastroenteric problem. Case 1 exhibited some subtle mental aberrations which are poorly understood. However, mental changes, including psychoses, have been reported in patients with hyperparathyroidism.[12] Two other patients with primary hyperparathyroidism recently observed at this hospital—a 62 year old man and an eight year old boy—presented more dramatic mental manifestations, including stupor, convulsions and coma.[13, 14] Case 2 had the additional problem of pregnancy. The premature birth of the infant of this pregnancy, plus the history that the preceding pregnancy had ended in a

miscarriage at seven months, suggests an adverse effect of hyperparathyroidism on pregnancy. A review of the limited observations which have been made regarding the effect of hyperparathyroidism on pregnancy indicates that this disease interferes with normal gestation.[15, 16] Also, it has been suggested that mothers of babies who have severe neonatal tetany should be investigated for the hyperparathyroidism.[15, 17] The diagnosis of hyperparathyroidism has been made on several occasions in women who had previously delivered premature infants, demonstrating protracted tetany. Recently a case has been reported of a three and a half year old child who had persistent hypoparathyroidism apparently resulting from maternal hyperparathyroidism.[18]

Summary

The histories of two patients with primary hyperparathyroidism are presented. The principal manifestations of the disease were related to the gastroenteric system and were associated with peptic ulcer.

Summario in Interlingua

Recentemente duo patientes con hyperparathyroidismo primari se presentava con le tableau clinic de ulcere peptic associate con symptomas gastroenteric de un duration de 20 annos. A causa de iste symptomas, ambe patientes esseva subjicite a resectiones gastric ante que le hyperparathyroidismo esseva recognoscite e corrigite. Symptomas gastroenteric es un manifestation major que es commun in hyperparathyroidismo primari. Tamen, le association de ulceres peptic con hyperparathyroidismo es appreciate minus generalmente. Le coexistentia de ulcere peptic con hyperparathyroidismo obscura le diagnose de hyperparathyroidismo, proque il es plausibile ascriber le symptomas gastroenteric al existentia del ulcere. Patientes con symptomas de ulcere que non responde satisfactorimente al therapia deberea esser examinate pro hyperparathyroidismo. Es presentate le historias de duo patientes con hyperparathyroidismo. Le manifestationes principal del morbo esseva relationate al systema gastroenteric e esseva associate con ulcere peptic.

BIBLIOGRAPHY

1. Albright, F., and Reifenstein, E. C., Jr.: The parathyroid glands and metabolic bone disease, 1948, The Williams and Wilkins Company, Baltimore.
2. Chaplin, H., Jr., Clark, L. D., and Ropes, M. W.: Vitamin D intoxication, Am. J. M. Sc. **221**: 369, 1951.
3. Dodd, K., Graubarth, H., and Rapoport, S.: Hypercalcemic nephropathy and encephalopathy following immobilization: case report, Pediatrics **6**: 124, 1950.
4. Gutman, A. B., Swenson, P. C., and Parsons, W. B.: The differential diagnosis of hyperparathyroidism, J. A. M. A. **103**: 87, 1934.
5. Rogers, H. M.: Parathyroid adenoma and hypertrophy of parathyroids, J. A. M. A. **130**: 22, 1946.
6. Rogers, H. M., Keating, F. R., Jr., Maelock, C. G., and Barker, N. W.: Primary hypertrophy and hyperplasia of the parathyroid glands associated with duodenal ulcer; report of an additional case with special reference to metabolic, gastrointestinal, and vascular manifestations, Arch. Int. Med. **79**: 307, 1947.
7. Black, B. M.: Hyperparathyroidism, 1954, Charles C Thomas, Publisher, Springfield, Illinois.
8. Hellstrom, J.: Primary hyperparathyroidism, Acta endocrinol. **16**: 30, 1954.

9. Schneider, R. W., and Robnett, A. H.: Diagnosis of obscure hyperparathyroidism, Cleveland Clin. Quart. **18**: 66, 1951.
10. Tsumori, H., Jensen, E., Hunnicutt, A. J., Foreman, N., and Kinsell, L. W.: Juvenile hyperparathyroidism in association with peptic ulcer, J. Clin. Endocrinol. and Metabolism **15**: 1141, 1955.
11. Schiffrin, M. J.: Relationship between parathyroid and the gastric glands in the dog, Am. J. Physiol. **135**: 660, 1942.
12. Fitz, T. E., and Hallman, B. L.: Mental changes associated with hyperparathyroidism; report of two cases, Arch. Int. Med. **89**: 547, 1952.
13. Lee, C. M., Jr., McElhinney, W. T., and Gall, E. A.: Unusual manifestations of parathyroid adenoma, Arch. Surg. **71**: 475, 1955.
14. Harmon, M.: Parathyroid adenoma in a child, Am. J. Dis. Child. **91**: 313, 1956.
15. Walton, R. L.: Neonatal tetany in 2 siblings, effect of maternal hyperparathyroidism, Pediatrics **13**: 227, 1954.
16. Spingarn, C. L., and Geist, S. H.: Hyperparathyroidism and pregnancy, J. A. M. A. **113**: 2387, 1939.
17. Van Arsdel, P. D., Jr.: Maternal hyperparathyroidism as a cause of neonatal tetany, J. Clin. Endocrinol. and Metabolism **15**: 680, 1955.
18. Bruce, J., and Strong, J. W.: Maternal hyperparathyroidism and parathyroid deficiency in the child, Quart. J. Med. **24**: 307, 1956.

MAIN BRANCH PULMONARY ARTERY THROMBOSIS WITH PULMONARY ABSCESS FORMATION: CASE REPORT*

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Abscess formation in an area of infarction is an unusual complication of thrombosis of the pulmonary arteries. Ring and Bakke[1] recently reported 21 cases of thrombosis of a main branch of the pulmonary artery, including seven cases with infarctions, only one of whom had an abscess. For this reason, reports of additional cases such as the one given here would appear to be of interest.

Case Report

History: When first seen in 1944 the patient, a 49 year old white man, reported a cough of six months' duration and two weeks of pain in the right portion of his chest. He had noted dyspnea on exertion for about six years, and had been on intermittent doses of digitalis.

Physical examination revealed a few râles and a friction rub over the right lower portion of the chest. X-rays of the chest showed accentuated hilar and bilateral bronchovascular markings. The heart was globular and moderately enlarged. The patient was treated symptomatically, and follow-up for one year showed a persistent cough, little sputum production, and a weight loss of 10 pounds.

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Hospitalization: The patient was next seen and admitted to hospital in 1951, with a diagnosis of congestive heart failure with hepatomegaly. He reported a chronic cough of seven years' duration and a loss of 40 pounds in the preceding six years. In the last six months he had been treated three times for heart failure.

Physical examination revealed the following significant findings: the anteroposterior diameter of the chest was increased; the heart was enlarged; the lungs contained many high-pitched rhonchi, and resonance was increased; the liver was enlarged four fingerbreadths below the costal margin and was tender, and there were clubbing and cyanosis of the fingers. X-rays of the chest showed pulmonary fibrosis and emphysema, and some pulmonary congestion. Right axis deviation and right ventricular hypertrophy were evidenced on the electrocardiogram. The hemoglobin was 18 gm.; arterial O_2 saturation was 82%, and arterial CO_2 was 68 vol.%.

Treatment by phlebotomy, digitalis and diuretics resulted in clinical improvement. After three weeks' hospitalization the discharge diagnosis was chronic pulmonary fibrosis and emphysema, pulmonary osteoarthropathy, and arteriosclerotic heart disease, Class II B.

The patient was re-admitted three months later for a dentigerous cyst of the left maxilla and removal of an impacted third molar. After one week he was discharged and was followed regularly in clinic.

In September, 1953, he had to stop work because of dyspnea and edema of the ankles. In June, 1955, he had moderate edema of the ankles and râles at both bases, despite taking daily digitalis and Mercuhydrin twice a week. A roentgenogram of the chest revealed large blebs in the right lower lung and a markedly enlarged heart. Phlebotomies were done in October and November, 1955, because of polycythemia.

The third admission, in December, 1955, was for increasing decompensation. On physical examination the patient appeared emaciated, dyspneic and cyanotic. The neck veins were distended, but the heart and lungs were unchanged. The liver, enlarged five fingerbreadths, was firm and moderately tender. Three plus clubbing of the fingers and toes was noted. An electrocardiogram showed auricular tachycardia, with variable block, and incomplete right bundle branch block. X-ray of the chest revealed emphysema and cor pulmonale, with greatly dilated pulmonary arteries and dilatation of the peripheral vascular markings.

The patient was treated for heart failure, and a program of bronchodilators by inhalation was started. A febrile episode, with increased amounts of foul greenish sputum, responded to Achromycin. He was discharged after 30 days, somewhat improved, with a diagnosis of pulmonary fibrosis and emphysema, bronchiectasis, pulmonary osteoarthropathy, and cor pulmonale with congestive failure.

The patient entered the hospital for the fourth time in February, 1956, because of increased dyspnea and sputum production. He was coughing frequently and appeared dyspneic, cyanotic and anxious. Fine moist râles were heard throughout both lung fields, and heart sounds were of poor quality. The liver was enlarged five fingerbreadths, and there was 4 plus pitting edema extending up to the knees. *Proteus vulgaris,* hemolytic *Staphylococcus aureus* and pneumococcus were cultured from the sputum. Electrocardiograms and x-ray examination of the chest showed no change.

One week after admission the patient's temperature rose to 103.4° F. He was cyanotic and somewhat disoriented, and there was an increase in the foul, thick sputum. Penicillin therapy lowered the temperature somewhat, and Achromycin brought prompt defervescence. X-rays, repeated three weeks after admission, revealed a large abscess in the apical segment of the left lower lobe of the lung, with an air-fluid level. Chloramphenicol was administered, and the regimen of bronchodilators and Bennett respirator was stepped up. The abscess cavity decreased in

size over the next three weeks, but the patient's course was progressively downhill. He became anuric terminally, and died in April, 1956, eight weeks after admission.

The final clinical diagnosis was pulmonary fibrosis and emphysema; bronchiectasis with secondary lung abscess, left lower lobe; and cor pulmonale with congestive heart failure.

Postmortem Findings: The pleural cavities were found to be obliterated by fibrous adhesions. The heart weighed 550 gm., and the apex was made up of right ventricle. The right atrium was dilated, and a small amount of adherent thrombus was found in its apex; the tricuspid valve measured 15 cm. in circumference. The right ventricle was dilated and measured up to 12 mm. in thickness at the base. The pulmonic valve measured 10 cm. in circumference. The main pulmonary artery was normal. A large, adherent thrombus was found in the left pulmonary artery about 2 cm. from its origin. The thrombus extended into the primary divisions. A smaller thrombus was found in the right main pulmonary artery, which, however, did not extend into the primary divisions. The left atrium and left ventricle were normal.

The left lung weighed 650 gm. In the apex of the left lower lobe there was an abscess cavity which measured 7 cm. in diameter. The wall was thickened uniformly to 2 cm. and was about half filled with thick, creamy material. No bronchial communication was found. The remaining portions of the left lung and the entire right lung showed a considerable amount of emphysema, with some fibrosis. Two blebs, approximately 2.5 cm. and 3 cm. in diameter, were noted in the right lower lobe. The femoral veins were not examined.

On histologic examination the heart was shown to be hypertrophied; sections of the thrombus from the left pulmonary artery revealed fibroblastic development. The lung revealed emphysema, some fibrosis, and thickened lining of several bronchi, with some infiltration of the walls by cells of chronic inflammation compatible with minimal bronchiectasis. The wall of the cavity contained thickened, hyalinized connective tissue, interspersed with considerable numbers of polymorphonuclear leukocytes and a few lymphocytes and plasma cells. The capillaries were dilated and filled with blood. Liver, spleen and kidney revealed the changes of chronic passive hyperemia.

Comment

Chronic pulmonary artery thrombosis is usually accompanied by severe dyspnea, progressive and intractable in nature. Although cyanosis is not always present, when it does occur it is marked. Cough, thoracic or epigastric pain, restlessness and mental confusion may also be present, although they occur less frequently. If the course of the disease is prolonged the pulmonary hypertension secondary to the diminished pulmonary vascular bed causes hypertrophy of the right ventricle and congestive failure.

Since these signs and symptoms also characterize chronic pulmonary fibrosis and emphysema, it is difficult to diagnose pulmonary artery thrombosis before death. Keating [2] has described characteristic x-ray findings of pulmonary artery thrombosis, including increased prominence of the pulmonary arteries and decreased peripheral vascular markings in the lungs. The increase in size of the pulmonary arteries was evident in our patient, but no decrease in peripheral vascular markings could be noted when the x-rays were reviewed. Electrocardiographic changes were masked by the bundle branch block.

Newer diagnostic methods have recently aided in making an antemortem diagnosis of chronic pulmonary artery thrombosis. Through the use of venogram studies, Briggs [3] found complete obstruction of the superior vena cava and

of the right main pulmonary artery, secondary to trauma, in a 30 year old man who was completely asymptomatic. Briggs also demonstrated that the O_2 consumption of his patient's right lung was zero. Carroll [4] was able to make the antemortem diagnosis of pulmonary artery thrombosis by cardiac catheterization and by angiocardiography.

The sudden appearance of lung abscess was an unusual feature in our case, for the patient was less toxic than would be expected. Since blebs had been noted on previous x-rays, the most likely possibility seemed to be an effusion into a bleb, secondary to nearby pneumonia. At autopsy, however, the thrombus was found to extend from the left main pulmonary artery into several branches, including the branch to the area of abscess. The right auricular thrombi were considered to be the source of the pulmonary artery thromboses.

The diagnosis of chronic pulmonary artery thrombosis has been reported more frequently in recent years, particularly in cases of chronic lung disease. Because the clinical picture is not always characteristic, the possibility of this diagnosis may be overlooked. Our experience, like that of other investigators, reëmphasizes the importance of its being included in the differential diagnosis whenever pulmonary fibrosis and emphysema are accompanied by lung abscess.

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SUMMARIO IN INTERLINGUA

Es reportate un caso de thrombose de un branca major del arteria pulmonar con formation de abscesso. Le patiente, un masculo de 61 annos de etate, habeva essite sub observation durante 12 annos a causa de symptomas de progressive fibrose pulmonar con emphysema. Therapia a digitalis e diureticos esseva necessari durante le ultime cinque annos del vita del patiente. Sex menses ante su morte, se notava edema con retention del alveos de pression in le region del cavilias, dyspnea post grados minimal de effortio, hepatomegalia, e marcate grados de digito hippocratic al manos e al pedes. Roentgenogrammas thoracic revelava marcate grados de fibrose pulmonar e plure grande bullas in le campo dextero-pulmonar. Le presentia de polycythemia necessitava phlebotomias. Durante su ultime menses le patiente deveniva emaciate e habeva frequente episodios de cyanose. Post un accesso de febre, le examine roentgenographic del thorace revelava le existentia de un grande abscesso in le campo sinistro-pulmonar. Le patiente moriva un mense plus tarde. Le definitive diagnose clinic esseva fibrose pulmonar e emphysema, bronchiectasis con secundari abscesso pulmonar, e corde pulmonal con congestive disfallimento cardiac.

Le constatationes necroptic includeva fibrose e emphysema pulmonar con corde pulmonal e alterationes secundari a congestive insufficientia cardiac. In plus, esseva trovate un micre thrombo adherente in le dilate atrio dextere, un grande thrombo adherente in le arteria sinistro-pulmonar que se continuava usque a in le divisiones primari, e un minus extense thrombo in le arteria pulmonar dextero-principal. Le abscesso del pulmon sinistre habeva un diametro de 7 cm. Le alimentation arterial de iste area habeva essite occludite per le thrombo del arteria sinistro-pulmonar.

Dyspnea de severitate progressive, cyanose, e hypertension pulmonar con corde pulmonal e congestive disfallimento cardiac es incontrate tanto in casos de thrombose de un branca major del arteria pulmonar como etiam in casos de chronic fibrose e emphysema pulmonar. Le differentiation inter iste duo conditiones es frequente-

mente difficile. Plure provate methodos pro le demonstration ante morte de thrombose del arteria pulmonar es citate ab le litteratura.

Le formation de abscessos in un area de infarcimento ha essite reportate in solmente pauc casos de thrombose del arterias pulmonar. Le manifestation subitanee de un abscesso pulmonar in chronic fibrose e emphysema pulmonar deberea inspirar le suspicion del presentia de thrombose de un branca major del arteria pulmonar como factor complicatori.

BIBLIOGRAPHY

1. Ring, A., and Bakke, J. R.: Chronic massive pulmonary artery thrombosis, Ann. Int. Med. **43**: 781–806, 1955.
2. Keating, D. R., Burkey, J. N., Hellerstein, H. K., and Feil, H.: Chronic massive thrombosis of pulmonary arteries, Am. J. Roentgenol. **69**: 208–220, 1953.
3. Briggs, G. W., Carlson, H. A., and Houseworth, J. H.: Superior vena cava obstruction with complete obstruction of the right main pulmonary artery, Am. Heart J. **48**: 288–292, 1954.
4. Carroll, D.: Chronic obstruction of major pulmonary arteries, Am. J. Med. **9**:175–185, 1950.

SEVERE AORTIC INSUFFICIENCY IN MARFAN'S SYNDROME *

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ALTHOUGH more than 10 years have elapsed since Baer, Taussig and Oppenheimer [1] first drew attention to involvement of the aortic wall as a complication of Marfan's syndrome, relatively few autopsy reports have been published with anatomic descriptions of the defect. Recent pathologic studies reported by McKusick [2] and others [3, 4] have stressed the variety of cardiovascular lesions that may be associated with this syndrome.

Over 50 autopsied cases of Marfan's syndrome have now been reported. In 1951 Marvel reviewed the findings in the 28 autopsied cases reported up to that time.[5] Table 1 summarizes the significant necropsy findings in 27 autopsied cases reported since Marvel's review. We wish to add a case of a patient who died of congestive heart failure due to severe aortic insufficiency with Marfan's syndrome.

Clinical manifestations of Marfan's syndrome have been frequently described in the medical literature, but many cases undoubtedly go clinically unrecognized because of the subtle way in which they present themselves. In a fully developed

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TABLE 1
Summary of Autopsied Cases of Marfan's Syndrome Reported since 1951

Author	Sex-Age at Death	Medionecrosis		Aneurysm-Type	Cause of Death and Associated Congenital Defect
		Aorta	Pulm. Art.		
Marvel and Genovese, 1951	Male 29 yrs.	Yes		Fusiform of aorta	Congestive failure
Moses, 1951	Female 52 yrs.	Yes	Yes	Saccular of aorta	Congestive failure and meningitis
	Female 26 yrs.	Yes		Aneurysm of aorta	Congestive failure
Whitfield et al., 1951	Male 35 yrs.	No		None	Congestive failure, myocarditis, hypoplastic aorta
Thomas et al., 1952	Male 32 yrs.	Yes		Dissecting	Congestive failure, dissecting aneurysm
	Male 26 yrs.	Yes		Fusiform and dissecting down to bifurcation of iliacs	Sudden with dissecting aneurysm
Tung and Liebow, 1952	Female 4 yrs.	Yes	No	Aneurysm of aortic sinuses	Congestive failure
	Female 36 yrs.	Yes	Yes	Dilated pulmonary artery	(?)(not clear)
Goyette and Palmer, 1953	Male 23 yrs.	Yes	No	Dissecting and "aneurysmal" of aorta	Congestive failure
Sloper and Storey, 1953	Female 24 yrs.	Yes		Diffuse dilatation of ascending aorta	Congestive failure
	Female 55 yrs.	Yes		Fusiform, ascending aorta	Congestive failure
Hedinger, 1953	Female 1 yr.	No		Cardiac hypertrophy, no aneurysm	Subdural bleeding
	Male 17 yrs.	No		Cardiac hypertrophy, no aneurysm	Chronic heart failure
Anderson and Pratt-Thomas, 1953	Female 23 yrs.	Yes	Yes	Fusiform of pulmonary artery with tear in intima	Congestive failure, patent ductus arteriosus
Traisman and Johnson, 1954	Male 9 mos.	Yes		Aneurysm ascending aorta	Pneumonia
	Male 10 yrs.	Yes		Fusiform of aorta with tears in intima	? Congestive failure
Reeh and Lehman, 1954	Male 25 yrs.	Not described		Dissecting aneurysm of aorta down to iliacs	Dissecting aneurysm
Maier et al., 1954	Male 33 yrs.	Yes		Saccular aneurysm of ascending aorta with tear and rupture	Sudden death with pericardial tamponade
Pygott, 1955	Female 44 yrs.	Not described		Saccular ascending aorta with multiple dissecting aneurysms	Congestive failure
McKusick, 1955	Male 40 yrs.	Yes		Fusiform of aorta	Congestive failure, coarctation of aorta
	Male 37 yrs.	Not described		Dilatation of ascending aorta with dissecting aneurysm	? Congestive failure, sudden death
	Male 24 yrs.	Not described		Dilatation of ascending aorta with dissection	Sudden death
	Female 8 mos.	Yes	Yes	Slight enlargement of pulmonary artery	Congestive failure, lung infection
	Female 26 yrs.	No		None	Congestive failure S.B.E.
	Male 24 yrs.	Yes		Dilated ascending aorta with dissecting aneurysm	Circulatory collapse, postoperative coarctation
Coffey et al., 1955	Male 33 yrs.	Not described		Dissecting aneurysm of aorta	Pulmonary edema; Coarctation of aorta
Bertrand et al., 1955	Male 2½ mos.	Not described		Heart normal	Bronch. pneumonia

case the diagnosis is readily suggested by the musculoskeletal and ocular abnormalities. The patients tend to be tall and thin, with disproportionately long distal extremities, muscular hypotonia, ligamentous relaxation, and lack of subcutaneous fat. The metacarpal and metatarsal bones, with their increased length, give the characteristic spider-like appearance to the extremities. The skull is long (dolichocephalic), with prominent supra-orbital ridges, large ears and a prominent jaw. The palate is high and arched, and the teeth may show irregularities in position and contour. Funnel-chest or pigeon-breast deformities are frequently present and may be associated with kyphosis or scoliosis.

The ocular abnormalities have been the subject of most of the attention given to this syndrome, and are well described in the ophthalmologic literature. Subluxation of the lens, iridodenesis, myopia and strabismus are the classic changes frequently described.[6] Many patients will of necessity wear thick-lensed glasses. When a sufficient number of these deformities are present a case is easily recognized, if thought of, but is just as easily missed by the unaware physician.

Because of the laxity of the ligaments, the patient's history may include previous hernia operations. Pes planus or other congenital abnormality of the feet is frequently noted. In spite of this ligamentous relaxation and the other physical changes, the ability of the patient to participate in athletic competition is not necessarily impaired. This was well demonstrated in our case, as the patient had been an expert bowler for many years. The long fingers in all probability were an asset to her attaining proficiency in this sport.

Case Report

A 37 year old white female entered Georgetown University Hospital in October, 1955, for cardiac evaluation after a two-year period of progressive dyspnea, orthopnea and chest pain. She had been considered to be in excellent health until two years prior to admission, when she suddenly experienced a severe retrosternal chest pain which radiated straight through to her back and to both arms. This occurred while she was at rest, and the pain subsided gradually over several hours. Several days later she was examined by her physician and a "heart murmur" was detected. Digitalis was prescribed. Interestingly, one week before the episode of chest pain a physician friend noted pulsations in her neck for the first time and advised her to have the matter investigated.

Prior to the episode of chest pain the patient had been an active bowler, and worked daily as a buyer for a large store, in addition to raising two young children. At no time had she experienced any respiratory distress or physical incapacity until the sudden onset of the present illness. Several months after the finding of the heart murmur, cardiac catheterization studies were performed at two separate hospitals and the only abnormality found was the presence of aortic insufficiency, diagnosed clinically. The tentative diagnosis when the patient was referred to Georgetown Hospital was aortic insufficiency, probably on a rheumatic basis, although a history of rheumatic fever was not obtainable.

During the year prior to admission, symptoms became progressively worse and the patient was forced to remain at rest because of chest pain on the slightest exertion (partly relieved by nitroglycerin), severe exertional dyspnea, marked weakness and occasional bouts of hemoptysis. Episodes of chest pain would often occur while at rest, and narcotics were frequently required for relief. During this time she had been on a good régime of medical management for her cardiac failure, but her course was progressively downhill.

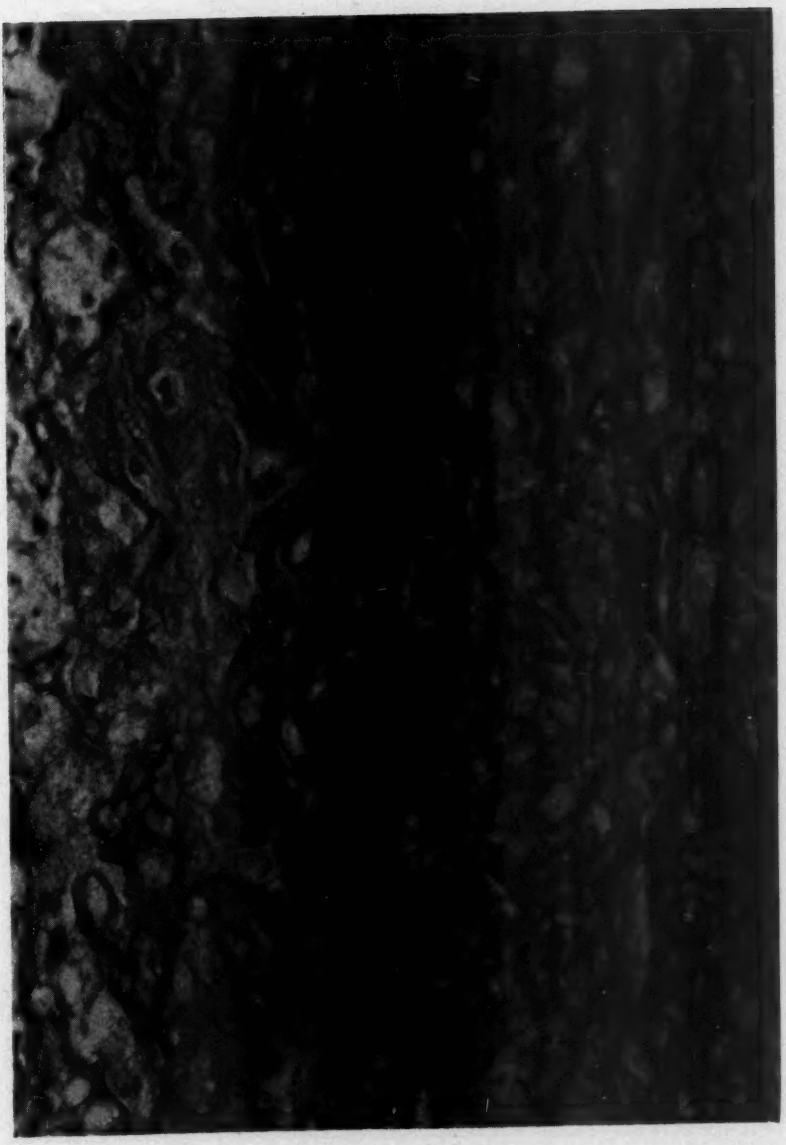

FIG. 1. Control. Internal elastic lamina of ascending aorta from 37 year old normotensive female. Verhoeff's elastic tissue stain × 280.

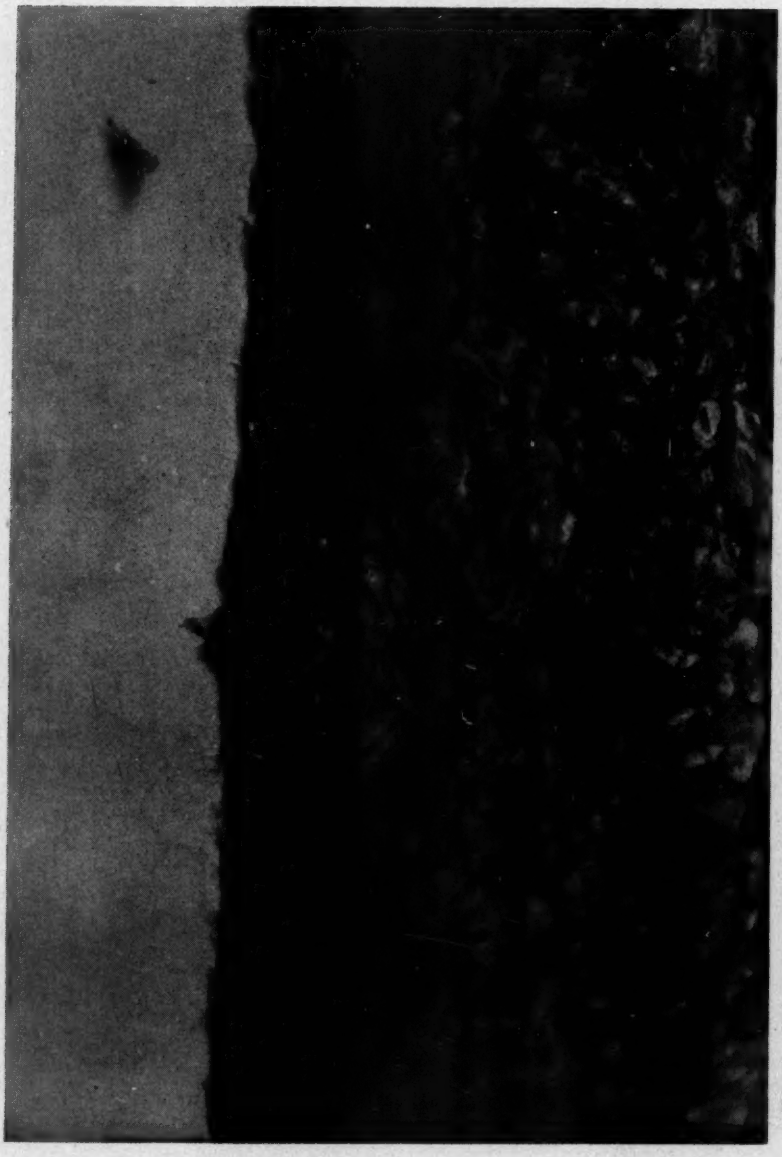

FIG. 2. Patient. Section through dilated ascending aorta, showing greatly widened, blurred and fibrillated internal elastic lamina. Verhoeff's elastic tissue stain × 280.

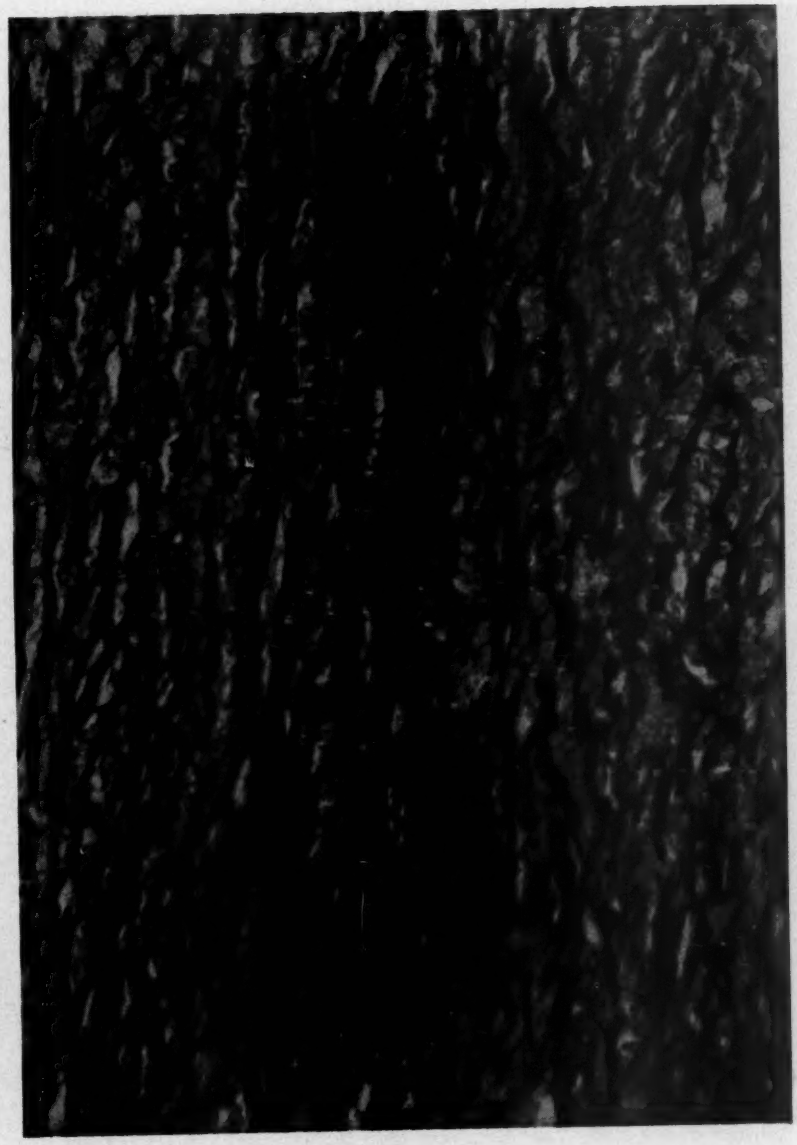

FIG. 3. Control. Showing media of ascending aorta from 37 year old normotensive female. Verhoeff's elastic tissue stain × 280.

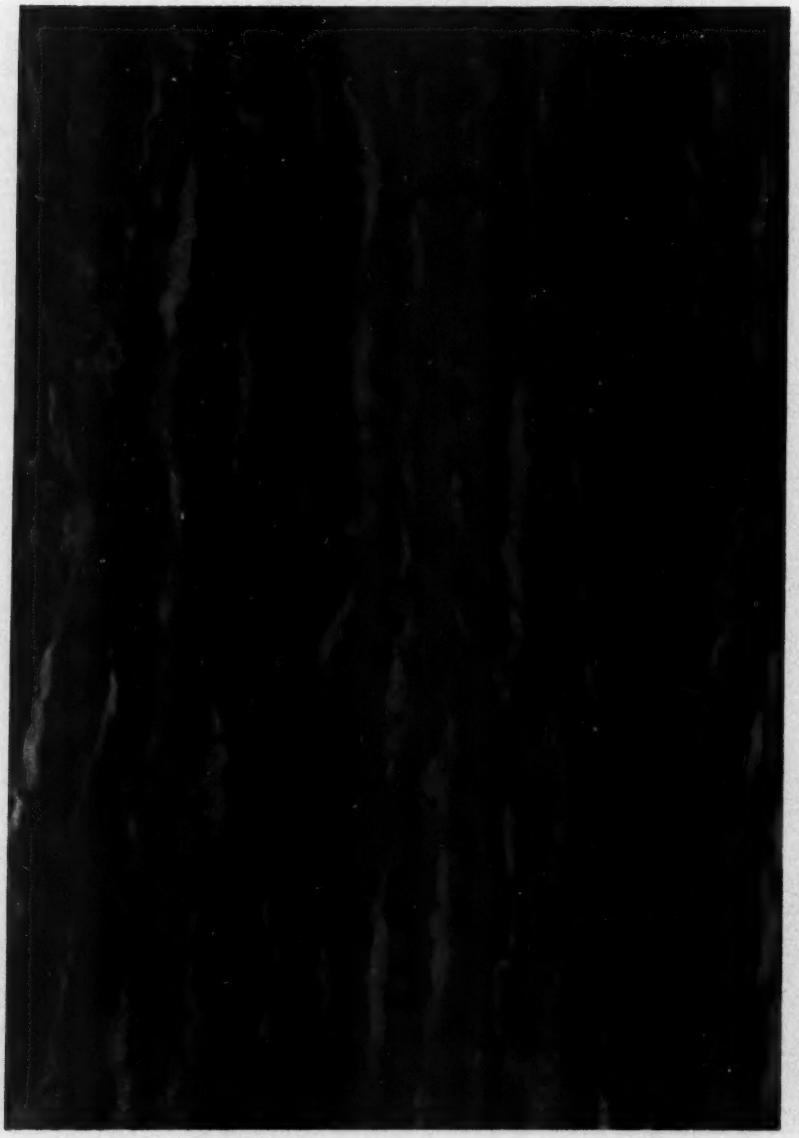

FIG. 4. Patient. Section through media of dilated ascending aorta, showing the wide separation of the broad elastic fibers. Verhoeff's elastic tissue stain × 280.

Past History: The patient had worn glasses since early childhood because of severe myopia. At the age of four she had had an operation for visual impairment and strabismus, at which time her family had been told by the surgeon that the eye difficulty might be on a congenital basis. There was no history of rheumatic fever or other serious childhood illness. The patient had always been physically active. Respiratory infections had not been frequent. There had been two uncomplicated pregnancies, at ages 28 and 29. Several physical examinations, from ages 21 to 23, had been passed successfully. A photograph of the patient's son, now age 10, showed that he had many of the typical physical characteristics of Marfan's syndrome.

Physical Examination: The patient was a tall, thin white female wearing thick-lensed glasses. She had prominent supra-orbital ridges. The skull was dolichocephalic. The extremities were long, with slim, tapering fingers and toes.

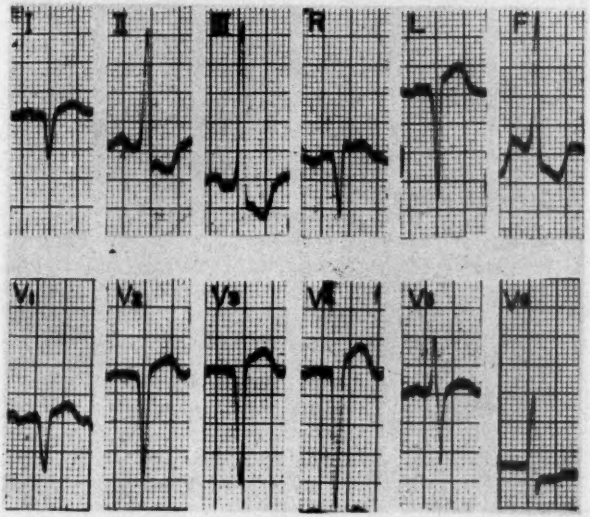

FIG. 5A. Electrocardiogram of patient shortly before death, showing first degree a-v block, left ventricular hypertrophy. Right axis deviation is attributed to the pectus excavatum deformity.

Blood pressure was 150/0 mm. of Hg in the arms and 190/50 mm. of Hg in the legs. The right pupil was eccentric and larger than the left. The right fundus was not visualized. The left fundus appeared normal, with marked myopia. The palate was high and arched, the ears were large, and a prominent funnel chest deformity was present. There were vigorous bilateral carotid artery pulsations. The lungs were clear to auscultation and percussion. The heart was enlarged to the left midaxillary line. The rhythm was regular, and there was a sharp, palpable pulmonic closure and a systolic heave over the midprecordium. A grade 4 diastolic aortic murmur was best heard along the left sternal border. A prominent ventricular diastolic gallop was present.

The electrocardiogram showed right axis deviation. Chest x-rays revealed the heart to be rotated to the left. Laboratory studies were otherwise within normal limits. Serology was negative.

The patient was being evaluated from the standpoint of possible insertion of the Hufnagel aortic valve prosthesis when she died suddenly on the fifth hospital day.

Necropsy: Gross Findings: The important findings related to the heart and aorta. The heart weighed 600 gm. The left ventricle was hypertrophied, measuring 1.8 cm. The proximal aorta was diffusely and symmetrically dilated, the greatest circumference being 16 cm. (normal, 8 to 9 cm.). The fusiform aneurysmal dilatation extended from the aortic valve to a distance of 10 cm. from the aortic ring. The aortic ring was considerably dilated (10 cm.), as were the sinuses of Valsalva. The aortic cusps were moderately sacculated but otherwise normal. The lungs were congested and edematous. The right pleural cavity contained 150 c.c. of straw-colored fluid.

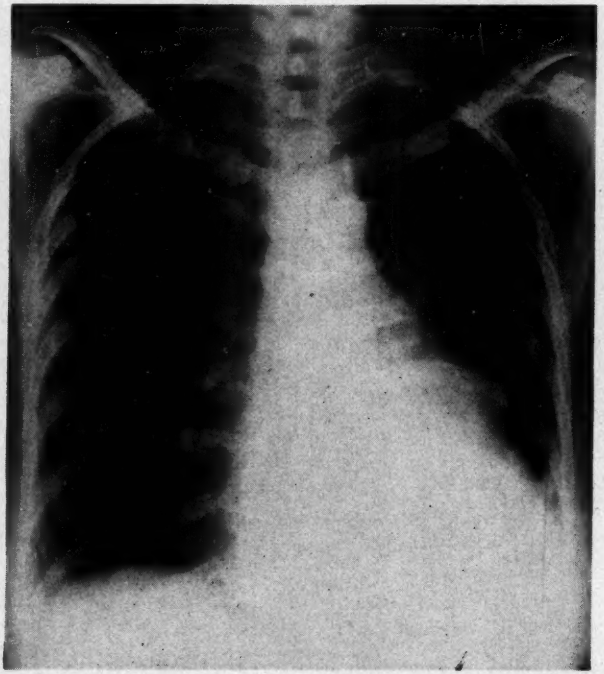

FIG. 5B. Chest x-ray of patient taken shortly before death, showing left ventricular enlargement and pulmonary congestion. The absence of any part of the cardiac shadow to the right of the sternum is characteristic of severe pectus excavatum.

Microscopic Examination: The left ventricular myocardium showed multiple foci of myocytolysis with replacement by connective tissue and capillary proliferation. The left anterior coronary artery showed two small, subintimal cystic areas of degeneration lined by loose, basophilic-staining material. Elastic tissue stains of the dilated proximal aorta were studied, using a 37-year old normotensive female as a control (Verhoeff's stain was found to be most satisfactory) (figures 1 and 2). The aortic wall was thicker than that of the control by one third. The internal elastic lamina was greatly widened, blurred and fibrillated (figure 2), differing markedly from the distinct thin plate of elastica seen in the control (figure 1). The elastic fibers in the media of the affected aorta were broad and frayed, and were considerably separated from each other. The separation was progressively greater as the ad-

ventitia was approached. The result of this wide spacing of the parallel-running elastic fibers was a separation by small cystic spaces of the muscle fibers of the media (figure 4). On H. and E. sections these spaces were seen to be filled with loose, basophilic-staining material. Disruption of elastic laminae could not be demonstrated. No abnormality of the collagenous fibers was present. There was a minimal ingrowth of vasa vasorum into the outer one fifth of the aorta. The adventitia was moderately and diffusely infiltrated with lymphocytes and a few plasma cells.

The liver, kidneys and spleen showed chronic passive congestion and edema.

Comment

The late microscopic changes which have been described in cases of Marfan's syndrome with aneurysmal dilatation of the ascending aorta have been summarized by McKusick as: (1) disruption of the elastic lamellae; (2) formation of conglomerate, disorganized masses of hyperplastic and hypertrophied smooth muscle fibers; and (3) formation of greatly dilated vascular channels penetrating the media from the adventitia.[2] In our case, features 1 and 2 were not prominent. Only minimal ingrowth of vasa vasorum into the media was present. The main features seen in the present case are: (1) the widened, frayed elastic plates of fibers and their separation, producing small cystic spaces within the muscle fibers; (2) the marked widening and fibrillation of the internal elastic lamina; and (3) the moderate diffuse infiltration of the adventitia with round cells.

It is possible that the aortic wall changes seen in this case represent an earlier stage in the degeneration process.

Discussion

Several hundred cases of arachnodactyly have been reported, and it is undoubtedly more common than is generally suspected. Cardiovascular complications in this syndrome are not uncommon. Rados [6] found 30% of 204 collected cases to have cardiovascular involvement or symptoms, and recent pathologic studies point up the variety of forms which such lesions may take.

In 1951 Marvel and Genovese [5] presented an excellent summary of the 28 cases of Marfan's syndrome with necropsy study which had been reported to that time. They added one case of their own. In the five years that have elapsed, an additional 26 necropsy reports have appeared,[2-4, 7-18] bringing the total to 55. This certainly reflects the increased attention being drawn to this syndrome.

In a review of these 26 necropsy reports, in addition to Marvel's case (total 27), a strikingly high incidence of cardiovascular involvement is apparent, with aortic insufficiency as the common, striking clinical finding. In contrast to earlier beliefs, such a congenital cardiac deformity as atrial septal defect is quite uncommon.

The pathologic defect underlying the aortic and pulmonary artery lesions so common in the necropsy findings consists of degenerative changes in the media which closely resemble the cystic medial necrosis of Erdheim. This change in the elastic and muscular tissue of the vessel wall may be present without gross lesion, but more commonly is associated with a saccular or dissecting aneurysm. Aortic or pulmonic insufficiency usually results from stretching and widening of the valve ring.

Cystic Medionecrosis: Definite medial changes were described in the wall of the aorta in 17 of the 21 cases in which microscopic examination was made (80%). A similar incidence was noted by Marvel [5] in his review of the first 28 necropsy reports. To date this finding has been absent in only six cases in which study of the aorta was made.

Cystic medionecrosis of the pulmonary artery was present in four of the cases in this review.[2, 3, 8, 10] The pulmonary artery was dilated in three of these instances,[2, 3, 10] and was of such severity in the case reported by Anderson and Pratt-Thomas [8] as to be directly responsible for the patient's death. This was the only case with an associated patent ductus arteriosus. Lillian [19] also described the association of patent ductus arteriosus and pulmonary artery aneurysms in a patient who was incidentally mentioned to have arachnodactyly. It is interesting to speculate as to the possible rôle a patent ductus may play in producing severe pulmonary artery aneurysmal dilatation when associated with medial degenerative changes.

Aortic Aneurysm: Aneurysmal dilatation of the ascending aorta or aortic sinuses was present in 18 of the 27 cases in this review, an incidence of 66%. Similar aneurysmal changes were described in the ascending aorta in 50% of the necropsies reviewed by Marvel.[5] We found true dissecting aneurysms of the aorta to be present in nine of the 27 necropsies. A total of 17 dissecting aneurysms have now been described in the 55 necropsy reports of Marfan's syndrome, an incidence of 30%.

In addition to the above lesions, coarctation of the aorta has been found in five of the necropsy reports to date,[2, 5, 16] and hypoplasia of the aorta in another report. Cardiac hypertrophy with myocardial fibrosis in the absence of valvular or aortic abnormalities is occasionally present.[7, 13]

The cardiovascular complications leading to death may occur even in infants less than one year of age.[2, 4] The ages of the necropsy-studied patients have ranged from two months [17] to 55 years.[12] There is no apparent sex predilection.

Death is usually due to congestive heart failure or dissecting aneurysm. As with aortic insufficiency of any etiology, sudden death often occurs. Tears in the intima at the aneurysm site may be found without dissections having occurred.[3, 4] Although dissection of the aorta is not uncommon in the aneurysmal dilatation, actual rupture of the aorta is rare.[14]

Heredity: This syndrome is now generally considered to be a heritable disorder of the connective tissue structures. It is not uncommon for several members of a family to be afflicted. The patient presented in this report has two children, one of whom has the typical bodily characteristics and marked myopia.

Of interest is the recent report by Whittaker and Sheehan [20] of two deaths due to dissecting aortic aneurysms occurring in a father and son. Neither patient had any of the clinical manifestations of Marfan's syndrome. However, at necropsy both cases showed medial degenerative changes in the aorta of the type commonly seen in Marfan's syndrome. Several other living members of the family have features typical of Marfan's syndrome, such as subluxation of the lens, high arched palate and irregular teeth. This report strongly suggests that the cardiovascular complication of the syndrome may occur without other defects being apparent.

Aortic Insufficiency: In view of the fact that an aortic diastolic murmur is

one of the earliest clinical signs of cardiovascular involvement, the differential diagnosis of this finding must be considered. Rheumatic heart disease remains the most common cause of aortic valvular insufficiency. Syphilitic aortic insufficiency is becoming less frequent with our present methods of treating this disease in its early stages. The murmur of aortic regurgitation may be found, due solely to severe arteriosclerosis [21] or marked diastolic hypertension.[22] In addition, acute or subacute bacterial endocarditis can initiate aortic regurgitation or aggravate a previously minor one. Other less common causes are congenital bicuspid aortic valves, especially when associated with coarctation of the aorta, penetrating or nonpenetrating chest trauma, severe physical stress,[23] dissecting or saccular aneurysms of the aorta, high interventricular septal defects, and aortic regurgitation associated with rheumatoid spondylitis.[25] Because of the frequency with which Marfan's syndrome is now recognized and the high incidence of aortic involvement in this disease, we feel that an increasing percentage of cases of aortic insufficiency will be ascribed to it. Undoubtedly many cases have been overlooked in the past. Steinberg and Geller have recently demonstrated aneurysmal dilatation of the aortic sinuses in three living patients with this syndrome by angiocardiography.[24]

Summary

A case of Marfan's syndrome with aortic involvement in a 37 year old patient is described. The patient died of congestive heart failure due to severe aortic regurgitation. The pathologic findings are presented, with a review of 27 previous necropsied cases of this syndrome. The clinical finding of aortic regurgitation should alert one to the possibility of Marfan's syndrome.

Summario in Interlingua

Un caso necropsiate de syndrome de Marfan es presentate. Le patiente esseva un feminina blanc de 37 annos de etate. Illa moriva de insufficientia sinistro-ventricular in consequentia de sever regurgitation aortic. Illa habeva multes del classic manifestationes clinic de syndrome de Marfan, incluse arachnodactylia, myopia e un historia de subluxation del lente, manco de grassia subcutanee, palato alte e arcate, grande aures, e prominente crestas supra-orbital. In plus, esseva presente un prominente deformitate infundibular del thorace. Le auscultation constatava sever regurgitation aortic in un corde allargate.

Le necropsia revelava un dilatation fusiforme de 10 cm de longor in le aorta ascendente. Isto produceva un relaxation del anulo aortic e insufficientia valvular. Le alterationes microscopic in le pariete aortic consisteva de allargation e fibrillation del interne membrana elastic, de large e frangiate fibras elastic in le media, e de micre spatios cystic in le fibras muscular del media.

Se trova in le litteratura plus que 50 reportos de necropsiate casos de syndrome de Marfan. In 1951 Marvel e Genovese summarisava le constatationes in le prime 28 casos publicate. Es presentate un revista de 27 casos necropsiate depost 1951. Es a notar un alte incidentia de affectiones cardiovascular in iste syndrome, con insufficientia aortic como communmente le plus frappante constatation clinic. Le morte resulta usualmente de congestive insufficientia cardiac o de aneurysma dissecante.

Medionecrose cystic in le pariete del aorta o del arteria pulmonar esseva presente in 80% del casos in que examines microscopic esseva facite.

Dilatation aneurysmal del aorta ascendente esseva trovate in 66% del 27 necropsias del presente revista e in 50% del prime 28 necropsias summarisate per Marvel.

Aneurysma dissecante in le aorta occurre in circa 30% del casos. Le syndrome es hereditari, e le datos nunc disponibile pare indicar le possibilitate de lesiones cardiovascular sin altere apparente manifestationes clinic.

Iste syndrome es un del minus commun causas de insufficientia aortic. Tamen, le constatation clinic del murmure de regurgitation aortic deberea esser prendite como adviso del possibilitate de syndrome de Marfan con affection aortic.

BIBLIOGRAPHY

1. Baer, R. W., Taussig, H. B., and Oppenheimer, E. H.: Congenital aneurysmal dilatation of the aorta associated with arachnodactyly, Bull. Johns Hopkins Hosp. **74**: 309–323, 1943.
2. McKusick, V. A.: The cardiovascular aspects of Marfan's syndrome: a heritable disorder of connective tissue, Circulation **11**: 321–342, 1955.
3. Anderson, M., and Pratt-Thomas, H. R.: Marfan's syndrome, Am. Heart J. **46**: 911–917, 1953.
4. Traisman, H. S., and Johnson, F. R.: Arachnodactyly associated with aneurysm of the aorta, Am. J. Dis. Child. **87**: 156–166, 1954.
5. Marvel, R. J., and Genovese, P. D.: Cardiovascular disease in Marfan's syndrome, Am. Heart J. **42**: 814–825, 1951.
6. Rados, A.: Marfan's syndrome (arachnodactyly coupled with dislocation of lens), Arch. Ophth. **27**: 477–538, 1942.
7. Whitfield, A. G. W., Arnott, W. M., and Stafford, J. L.: "Myocarditis" and aortic hypoplasia in arachnodactylia, Lancet **1**: 1387–1391, 1951.
8. Moses, M. F.: Aortic lesions associated with arachnodactyly, Brit. M. J. **2**: 81–84, 1951.
9. Thomas, J., Brothers, G. B., Anderson, R. S., and Cuff, J. R.: Marfan's syndrome; a report of three cases with aneurysm of the aorta, Am. J. Med. **12**: 613–618, 1952.
10. Tung, H. L., and Liebow, A. A.: Marfan's syndrome. Observations at necropsy with special reference to medionecrosis of the great vessels, Lab. Invest. **1**: 382–406, 1952.
11. Goyette, E. M., and Palmer, P. W.: Cardiovascular lesions in arachnodactyly, Circulation **7**: 373–379, 1953.
12. Sloper, J. C., and Storey, G.: Aneurysms of the ascending aorta due to medial degeneration associated with arachnodactyly (Marfan's disease), J. Clin. Path. **6**: 299–303, 1953.
13. Hedinger, Von Chr.: Herz- und Gefabveranderungen bei Marfanschen Syndrom (Arachnodaktylie), Schweiz. Ztschr. allg. Path. **16**: 977–982, 1953.
14. Maier, N. C., Rubli, J. M., Schaub, F., and Hedinger, C.: Cardiale Storungen bein Marfanschen Syndrom, Cardiologia **24**: 106–110, 1954.
15. Reeh, M. J., and Lehman, W. L.: Marfan's syndrome (arachnodactyly) with ectopia lentis, Tr. Am. Acad. Ophth. **58**: 212–216, 1954.
16. Coffey, J. H., Barker, D. E., and Friedlander, J. H.: Dissecting aneurysm with Marfan's syndrome, Texas State J. Med. **51**: 79–81, 1955.
17. Bertrand, I., Weill, J., and Burtin, P.: Histopathologie due cerveau et des globes oculaires dans un cas d'arachnodactylie du nourrisson (Maladie de Marfan), Rev. neurol. **92**: 137–139, 1955.
18. Pygott, F.: Arachnodactyly (Marfan's syndrome) with a report of two cases, Brit. J. Radiol. **28**: 26–29, 1955.
19. Lillian, M.: Multiple pulmonary artery aneurysms, Am. J. Med. **7**: 280–287, 1949.
20. Whittaker, S. R. F., and Sheehan, J. D.: Dissecting aortic aneurysm in Marfan's syndrome, Lancet **2**: 791–792, 1954.
21. Fenichel, N. M.: Arteriosclerotic aortic insufficiency, Am. Heart J. **40**: 117–124, 1950.

22. Garvin, C. F.: Functional aortic insufficiency, Am. Heart J. 13: 1799–1803, 1940.
23. Bean, W. B., and Mohaupt, F. Y.: Rupture of an aortic valve, J. A. M. A. 150: 92–93, 1952.
24. Steinberg, I., and Geller, W.: Aneurysmal dilatation of aortic sinuses in arachnodactyly: diagnosis during life in three cases, Ann. Int. Med. 43: 120–132, 1955.
25. Schilder, D. P., Harvey, W. P., and Hufnagel, C. A.: Rheumatoid spondylitis and aortic insufficiency, New England J. Med. 255: 11–17 (July 5) 1956.

PHEOCHROMOCYTOMA OF THE ADRENAL GLAND WITH GRANULOSA CELL TUMOR AND NEUROFIBROMATOSIS: REPORT OF A CASE WITH FATAL OUTCOME FOLLOWING ABDOMINAL AORTOGRAPHY *

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Pheochromocytoma today cannot be considered an unusually rare tumor, since numerous isolated cases as well as small series have been reported. In 1952 Aaron [1] stated that about 300 cases had been published, but that they probably represent but a small fraction of the actual number.

The association of pheochromocytoma with a malignant neoplasia, however, is much more infrequent. Four cases have been reported associated with neuroblastomas.[2, 3, 4, 5] One case had a "neurogenic sarcoma," [6] one a carcinoma of the rectum,[7] and another a neurofibromatosis with "malignant degeneration." [8] The second case of Mandeville and Sahyoun [9] and the recent one of Tamura and Lawrence [10] will not be considered here, since they are both cases of malignant pheochromocytomas, the former associated with bronchogenic carcinoma and the latter with a malignant schwannoma of the thorax. The total cases of pheochromocytoma associated with malignant neoplasia at the present time stand at seven, to the best of our knowledge.

In 1953 Glushien and collaborators [11] reviewed the literature on pheochromocytomas associated with the neurofibromatosis of von Recklinghausen. They found 17 cases and added one, making a total of 18 cases reported to that date. Since then one more case has been reported, by Koonce and collaborators,[12] which presents an interesting fact: it is, to the best of our knowledge, the only one prior to ours of death following abdominal aortography. Koonce's case was that of a 50-year old white soldier who died in shock due to retroperitoneal hemorrhage 36 hours after aortography was performed. Bilateral pheochromocytomas were found at autopsy, and total pressor substances (epinephrine) were determined on the right adrenal tumor. The total pressor substances were 2,318 mg.

Case Report

A thirty-eight year old Negro female was admitted to the Ohio State University Health Center on August 9, 1954. Family history was not contributory except for

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results were not diagnostic of pheochromocytoma (figure 1). This negativity of the benzodioxane test in the presence of pheochromocytoma of the adrenal has been reported in several instances.[1]

A Regitine test [14] was performed on August 18 and was interpreted as diagnostic of pheochromocytoma (figure 1).

Urograms and radiologic examination of the chest, gastrointestinal tract and skull were all within normal limits.

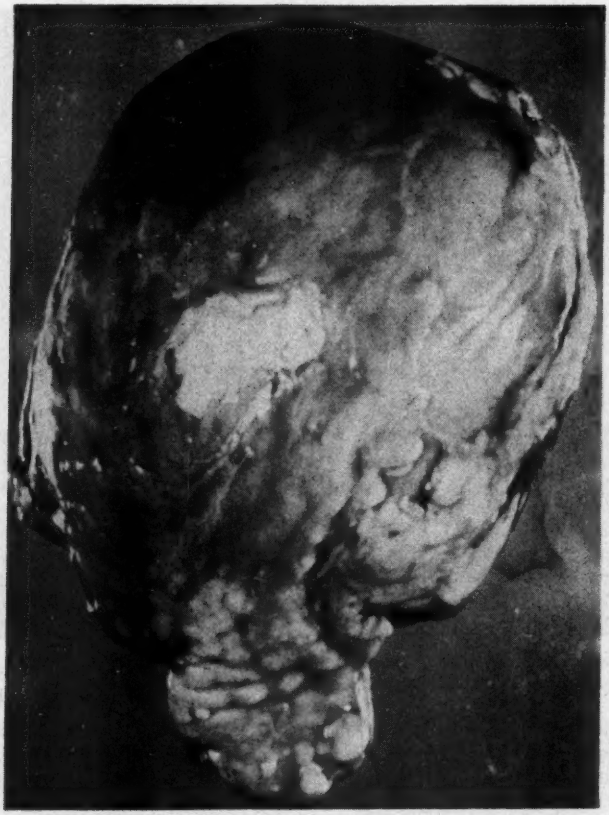

FIG. 3. Pheochromocytoma of the left adrenal gland. The remnant of normal adrenal appears at the lower portion of the photograph.

With the diagnosis of hypertension due to physiologically active pheochromocytoma, the patient was transferred to the Surgical Service where, on August 23, an abdominal aortogram was performed. Preanesthesia medication consisted of 75 mg. intramuscularly of Demerol and 200 mg. of Nembutal. Anesthesia was started at 3:30 p.m., using 1% Procaine locally. A needle was placed in the aorta 1 cm. below the twelfth rib. Sixty cubic centimeters of 70% Diodrast were injected, and four films were taken with the patient in the prone position. The films failed to visualize the tumor. Under Pentothal anesthesia (2.5% per cubic centimeter; 6 c.c. intra-

venously) a second needle was placed in the aorta and the injection was repeated, with excellent visualization of the superior and inferior mesenteric arteries, both renal and iliac arteries, and a clearly visualized tumor at the upper pole of the left kidney, with increased vascularization of the region. The findings were diagnostic of left adrenal tumor. The patient was returned to the Recovery Room in apparent good condition at 4:00 p.m. At 4:30 p.m. her blood pressure was 100/?; pulse, 120; respiration, 20 per minute. She developed tachycardia, Cheyne-Stokes respirations, dilatation of the pupils and profuse sweating. Her blood pressure rose steadily—at 5:30 p.m. it was 188/104 mm. Hg; pulse, 166 per minute, weak and feeble. She was digitalized without benefit, and died at 6:45 p.m.

Autopsy Findings: Complete autopsy was performed three hours after death on the unembalmed body. Only the pertinent data are given. The external examination disclosed the neurofibromatosis described clinically, as well as moderate oozing of blood from the vagina. There was no fluid in the abdominal cavity. The peri-

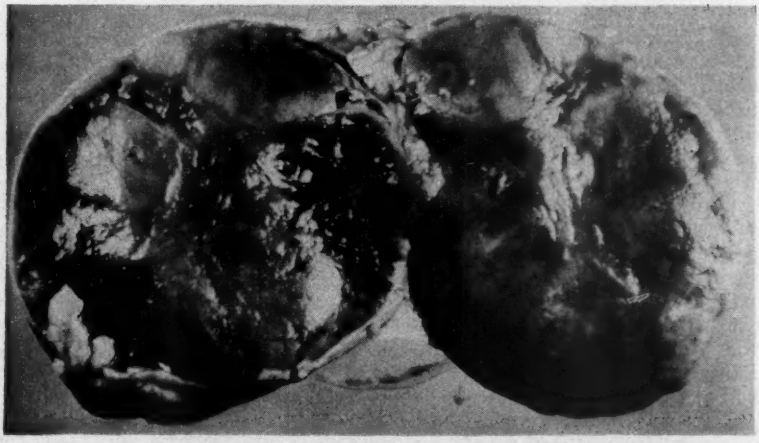

FIG. 4. Pheochromocytoma of the left adrenal gland. Cross-section of the tumor. Areas of hemorrhage and necrosis are evident. A small, thin cortex is visible in some areas.

toneum, omentum and mesentery were studded with tumor nodules ranging from a few millimeters up to 3 cm. in diameter. On cross-section these tumor nodules were firm, rubbery and a yellowish pink, with central honey-combed areas. Numerous similar nodules were present in the retroperitoneal space. Some of these nodules were of considerable size: one, adjacent to the right kidney, measured 9 by 6 by 4 cm. and weighed 130 gm. Similar tumor nodules replaced the ovaries and ovarian ligaments (figure 2).

The right adrenal gland weighed 4 gm. and was not remarkable grossly. The left adrenal gland was surrounded by a 10 by 10 by 10 cm. hematoma which extended over the superior pole of the left kidney. The hematoma was composed of fresh and partially clotted blood. After careful removal of the hematoma the adrenal gland presented a well encapsulated, brown-red tumor which measured 5 cm. in diameter. On section the tumor was brown-red and soft, and surrounded by a 0.5 cm. thick rim of yellow cortex in some areas. In other areas the tumor presented fresh hemorrhages and evidence of necrosis. The remnant of the adrenal gland measured 4 by 1.5 cm. and was represented by the lower pole of the gland. The total weight of the left adrenal, including the tumor, was 75 gm. (figures 3 and 4).

The remainder of the organs, including the central nervous system, were not remarkable grossly.

Sections of the adrenals were fixed in Zenker's solution, the remaining organs in 10% formalin. All sections were stained with hematoxylin-eosin.

Histologically, the adrenal tumor was composed of large cells with indistinct boundaries and eosinophilic, abundant granular cytoplasm. Many cells contained brown pigment in the cytoplasm. The nuclei were large, vesicular, round to oval, sometimes multiple and with a fine chromatin network. The nucleoli were prominent, round and eosinophilic. Mitotic figures were rare, and multiple areas of necrosis and fresh hemorrhages were evident throughout the sections. The tumor was supported by a delicate network of collagenous tissue with numerous capillaries and small blood vessels, and was limited peripherally in some sections by normal adrenal cortex with abundant lipid contents. The presence of brown granules (chromaffin reaction) in the cytoplasm is considered by some authors as absolutely necessary for histologic diagnosis of a pheochromocytoma [15] (figure 5).

All sections from the peritoneal and other areas involved by the other tumor showed a variable histologic pattern. In some sections the tumor was composed of sheets of small cells with scanty, eosinophilic cytoplasm and round to oval, usually vesicular nuclei (figure 6). The cellular boundaries were irregular and somewhat indistinct. The nuclear chromatin was fine and reticular, and the nucleoli were small. Abnormal mitotic figures were extremely rare, but hyperchromatism and even pyknosis were seen in several areas. Furthermore, the high degree of malignancy of the tumor was evident by the frequent nests of tumor cells in the lumen of lymphatics. The sheets of tumor cells were separated in compartments by thick, coarse strands of fibrous connective tissue. In many areas a small acinar structure appeared in the middle of solid sheets of tumor cells, while in others the histologic pattern was composed of acinar structures lined by a single layer of tumor cells containing in their lumen bright eosinophilic, colloid-like material. These areas closely resembled the histology of thyroid. When these acini appeared dilated and almost cystic, the large quantities of colloid material in their lumen apparently "flattened" the tumor cells, which then appeared spindle-shaped. The transition between the solid and the cystic pattern was usually gradual, but some nodules were strictly solid while others were mostly cystic. In the areas where acini were cystlike they lay one beside the other without appreciable supporting stroma, while in other areas, fine bundles of fibrous connective tissue formed the supporting structure (figures 7 and 8). In spite of examination of multiple blocks, the ovaries could not be identified microscopically.

The histologic pattern of this tumor was believed to be compatible with "granulosa cell tumor," [16] with total replacement of the ovaries and multiple abdominal metastases.

Sections of the skin disclosed the typical neurofibromatosis of von Recklinghausen. Sections of heart, lungs, spleen, liver, pancreas, gall-bladder, gastrointestinal tract, kidneys, right adrenal, bladder, uterus, cervix, vagina, thyroid, hypophysis, skeletal muscle, central nervous system, optic nerves, optic chiasm and bone marrow (vertebral and costal) were also examined. Secondary diagnosis consisted of moderate pulmonary edema, acute passive congestion of the spleen, and minimal glomerulitis of the kidneys.

Vasopressor Substances Determination: Half of the adrenal tumor and the entire heart were submitted to the Laboratory of Endocrinology. Colorimetric determinations of pressor substances were done using von Euler's method.[17] In the adrenal tumor the total pressor substances were 22.2 mg. per gram of tumor tissue, or a total of approximately 1,650 mg. (normal, 0.25 to 0.70 mg. per gram of adrenal tissue).[18] In the heart, with the same method used but concentrating with aluminum hydroxide,

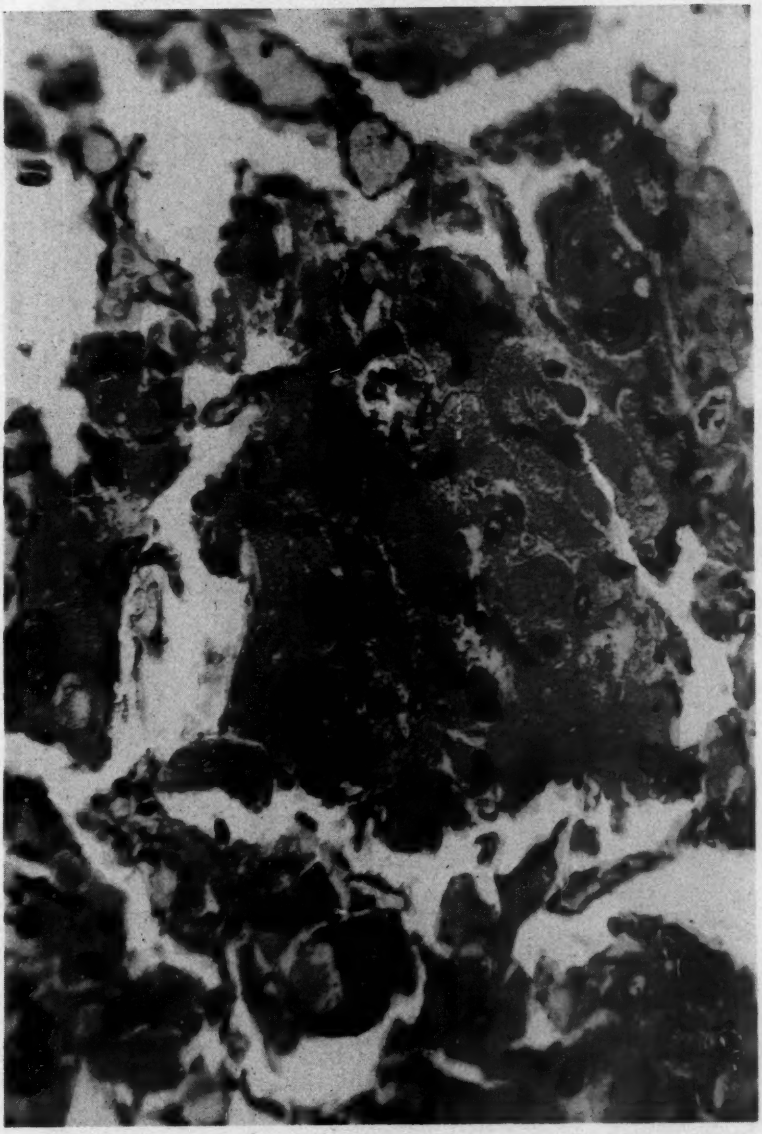

FIG. 5. Pheochromocytoma of the adrenal gland. Microscopic aspect. × 440.

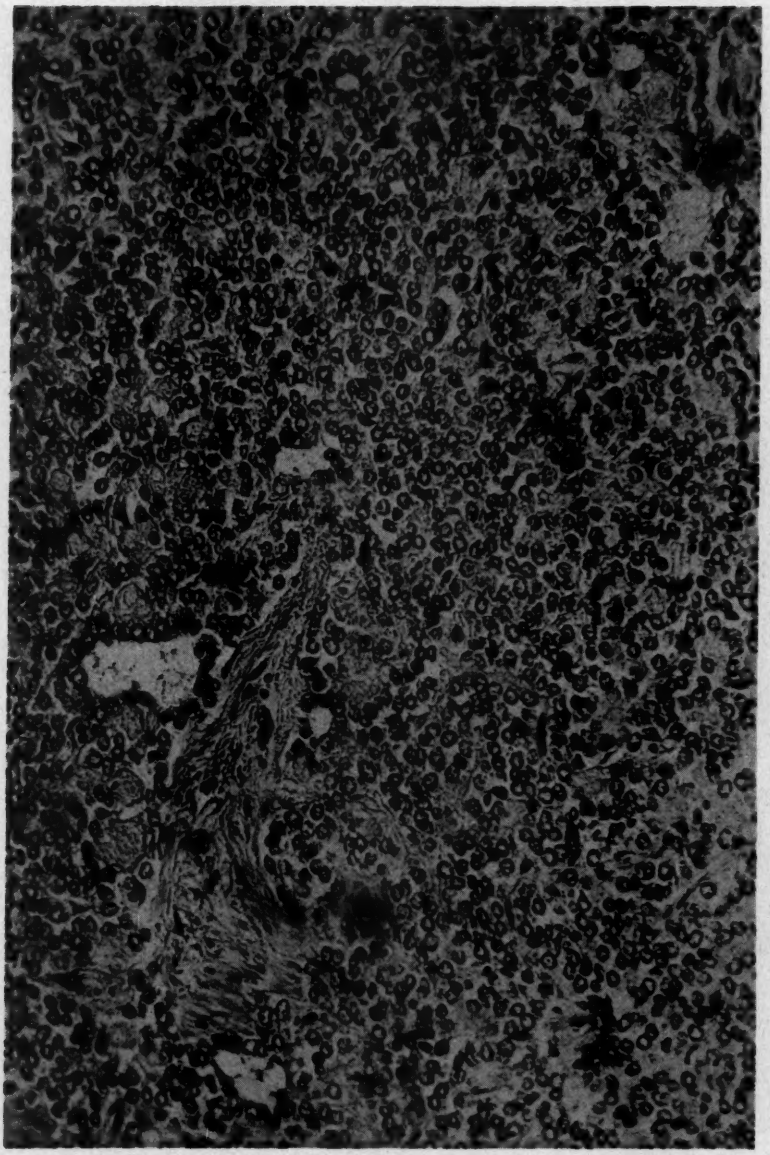

FIG. 6. Granulosa cell tumor. Area of almost solid pattern. An occasional acinar structure is present. ×250.

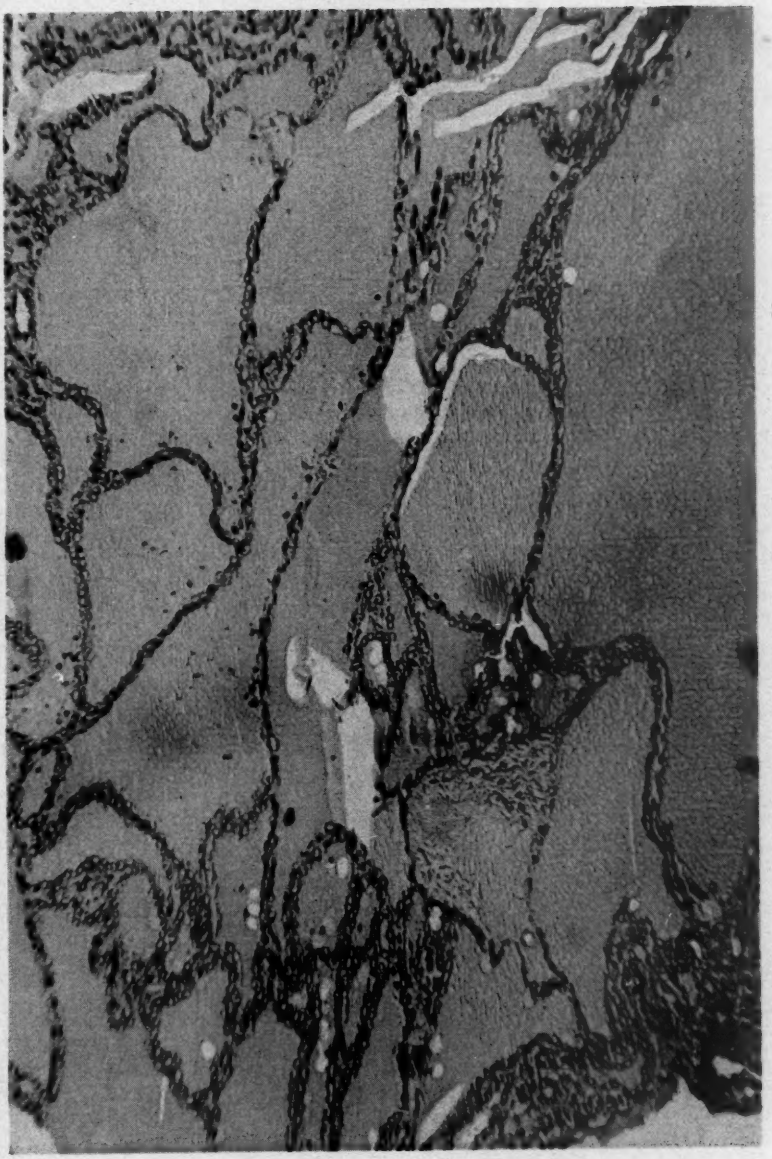

FIG. 7. Granulosa cell tumor. Area of acinar pattern. × 90.

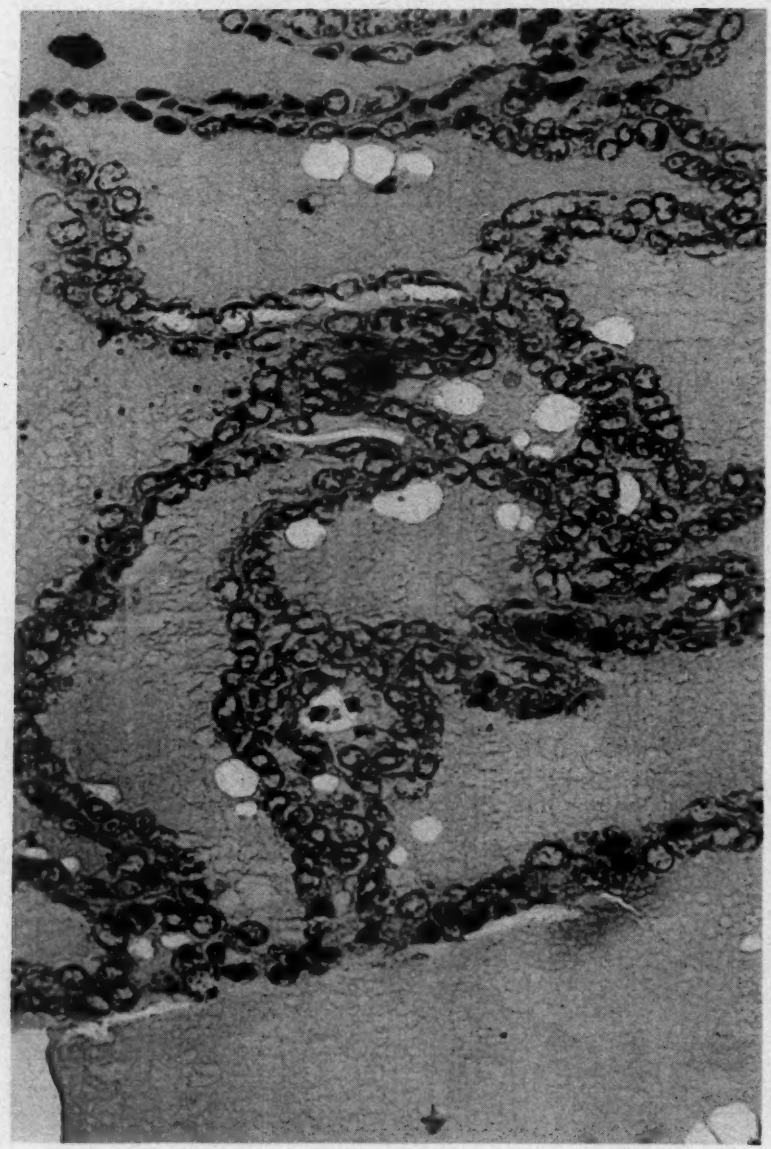

FIG. 8. Granulosa cell tumor. Area of acinar pattern. Note that in many acini the cells appear flattened. ×440.

the total catechol was 1.46 μg per gram of heart tissue (0.57 μg per gram of adrenalin and 0.89 μg per gram of noradrenalin). Normal total catechol values are approximately 0.25 μg per gram of tissue, with an arbitrary upper limit of 0.6 μg per gram of tissue, predominantly noradrenalin.[18]

Comment

The present case emphasizes the danger of abdominal aortography in pheochromocytoma, since the possibility of trauma in the adrenal region, with liberation of large quantities of pressor substances and acute heart failure, must be kept in mind at all times. It is now well recognized that abrupt manipulation of pheochromocytoma at surgery or physical examination can produce the same reaction, and even spontaneous hemorrhages have been shown to have the same effect.[19] To demonstrate the localization of a pheochromocytoma prior to surgery is not absolutely necessary. Both adrenal regions should be explored in all cases; otherwise, the possibility of missing a bilateral pheochromocytoma is not improbable, since in 20% of the cases reported the tumor is multiple and in almost half of the cases is bilateral.[1]

Summary

1. A case of pheochromocytoma, malignant granulosa cell tumor and neurofibromatosis is reported. Pheochromocytoma has already been reported in association with malignant neoplasms in seven cases, but never with granulosa cell tumor. It has been reported associated with neurofibromatosis on 18 previous occasions.

2. A search of the literature discloses only one case of death following abdominal aortography. The mechanism of death appears to be adrenalinic crisis precipitated by intra-adrenal and/or periadrenal hemorrhage, with liberation of large amounts of pressor substances (adrenalin and noradrenalin).

3. Pressor substances were determined post mortem, using the colorimetric method of von Euler and Hamberg. They were significantly elevated in both the adrenal tumor and the heart.

Addendum

Since this report was submitted an additional case of death following abdominal aortography has appeared. Extensive periadrenal hemorrhage and bleeding in a right adrenal pheochromocytoma were found at the autopsy of a 23 year old female who died in peripheral collapse 24 hours after aortography.[20]

Acknowledgment

I am indebted to Dr. E. von Haam for permitting the report of this case, to Dr. J. M. Bloodworth for the determination of vasopressor substances, to Dr. J. Turner for helpful criticism, and to Mrs. G. Roberts for the secretarial work.

Summario in Interlingua

Es reportate un caso de un negra de 38 annos de etate con un pheochromocytoma del glandula adrenal sinistre, maligne tumor de cellulas granulose, e neurofibromatosis. Pheochromocytoma ha essite reportate in association con neoplasma maligne in septe

previe casos sed nunquam in association con tumor de cellulas granulose. Illo ha essite reportate in association con neurofibromatosis in 18 previe occasiones.

Un test a Regitina esseva effectuate e considerate como diagnostic pro pheochromocytoma. Aortographia abdominal esseva executate. Un hora e medie plus tarde le patiente disveloppava tachycardia, profuse grados de transspiration, dilatation del pupillas, e respiration de Cheyne-Stokes. Alora illa moriva.

Le necropsia revelava un tumor de cellulas granulose que habeva afficite le peritoneo, le mesenterio, le omento, le spatio retroperitoneal, le ovarios, e le ligamentos ovarian. Un pheochromocytoma sinistro-adrenal con hematoma circumjacente esseva etiam trovate. Le total substantias pressori in le tumor adrenal esseva 1.650 mg. Le catechol total esseva 1,46 μg per g de histo cardiac (0,57 μg per g de adrenalina e 0,89 μg per g de noradrenalina). Le diagnose clinic de neurofibromatosis esseva confirmate.

Un scrutinio del litteratura revelava un altere caso de pheochromocytoma in que le morte del patiente sequeva le effectuation de aortographia abdominal. Le mechanismo mortal es apparentemente un crise adrenalinic precipitate per hemorrhagia intra-adrenal e/o periadrenal, con le liberation de grande quantitates de substantias pressori (adrenalina e noradrenalina). Le datos indica que le uso de iste methodo in le presentia de un functionante pheochromocytoma es riscose e probabilemente contraindicate.

BIBLIOGRAPHY

1. Aaron, H.: Pheochromocytoma, *in* Monographs in medicine, edited by W. B. Bean, Series I, 1952, The Williams & Wilkins Company, Baltimore, pp. 179–224.
2. Lewis, D., and Geschickter, C. F.: Tumors of the sympathetic nervous system: neuroblastoma, paraganglioma and ganglioneuroma, Arch. Surg. **28**: 16, 1934.
3. Wahl, H. R., and Craig, P. E.: Multiple tumors of the sympathetic nervous system. Report of a case showing a distinct ganglioneuroma, a neuroblastoma, and a cystic calcifying ganglioneuroblastoma, Am. J. Path. **14**: 797, 1938.
4. Wahl, H. R., and Robinson, D.: Neuroblastoma of the mediastinum with pheochromoblastomatous elements, Arch. Path. **35**: 571, 1943.
5. Fernando, P. B., Cooray, G. H., and Thanabalasundram, R. S.: Adrenal pheochromocytoma with neuroblastomatous elements. Report of a case with autopsy, Arch. Path. **52**: 182, 1951.
6. Lichtenstein, B. W.: Neurofibromatosis (von Recklinghausen's disease of the nervous system). Analysis of the total pathological picture, Arch. Neurol. and Psychiat. **62**: 822, 1949.
7. Berkheiser, S. W., and Rappoport, A. E.: Unsuspected pheochromocytoma of the adrenal. Report of five cases, Am. J. Clin. Path. **21**: 657, 1951.
8. Rossum, B. C., and Barry, M. W.: Paraganglioma in suprarenal medulla with neurofibromatosis, Nebraska M. J. **15**: 243, 1930.
9. Mandeville, F. B., and Sahyoun, P. F.: Benign and malignant pheochromocytomas with necropsies: benign case with neurofibromatosis and cavernous hemangioma of the 4th ventricle; malignant case with widespread metastases and bronchogenic carcinoma, J. Urol. **62**: 93, 1949.
10. Tamura, P. Y., and Lawrence, L. T.: Multiple tumors of the sympathetic system. A report of a case of malignant schwannoma associated with functioning malignant pheochromocytoma, Cancer **9**: 293, 1956.
11. Glushien, A. S., Mansuy, M. M., and Littman, D. S.: Pheochromocytoma. Its relationship to the neurocutaneous syndromes, Am. J. Med. **14**: 318, 1953.
12. Koonce, D. H., Pollock, B. E., and Glassy, F. J.: Bilateral pheochromocytoma associated with neurofibromatosis. Death following aortography, Am. Heart J. **44**: 901, 1952.

13. Goldenberg, M., Snyder, C. H., and Aaron, H.: New test for hypertension due to circulating epinephrine, J. A. M. A. **135**: 971, 1947.
14. Emlet, J. R., Grimson, K. S., Bell, D. M., and Orgain, E. S.: Use of piperoxan and Regitine as routine test in patients with hypertension, J. A. M. A. **146**: 1383, 1951.
15. Karsner, H. T.: Tumors of the adrenal, Atlas of Tumor Pathology, Section VIII, Fascicle 29, 1950, Armed Forces Institute of Pathology, Washington, D. C.
16. Novak, E.: Gynecology and obstetrics: pathology, Third Edition, 1952, W. B. Saunders Co., Philadelphia, pp. 404–412.
17. Von Euler, V. S., and Hamberg, V.: Colorimetric determinations of noradrenaline and adrenaline, Acta physiol. Scandinav. **19**: 74, 1949.
18. Bloodworth, J. M.: Personal communication.
19. Lehman, D. J., and Rosof, J.: Massive hemorrhage into an adrenal pheochromocytoma, New England J. Med. **254**: 474, 1956.
20. Saltz, N. J., Luttwak, E. M., Schwartz, A., and Goldberg, G. M.: Danger of aortography in the localization of pheochromocytoma, Ann. Surg. **144**: 118, 1956.

LONG CONTINUING JAUNDICE FOLLOWING MINIMAL CHLORPROMAZINE (THORAZINE) MEDICATION*

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MANY reports have appeared regarding the occasional occurrence of jaundice in patients who are receiving or have recently received chlorpromazine. It is rather generally stated that the incidence of such jaundice is very low, around 1% or less, although some clinicians have had a less favorable experience, such as the three cases of jaundice in 26 patients reported by Isaacs, Macarthur and Taylor.[1] Our own experience, though meager, has been of a similarly frequent incidence of jaundice. The severity of the case here reported has given us caution in any free employment of the drug. While the conclusions voiced as to the relative infrequency of jaundice and its transient character may be generally true, there is no certainty that, either by small dosage or brief period of administration, prolonged and gravely disquieting jaundice can be avoided. It is to stress this point, one not readily garnered in reading the many favorable clinical evaluations of the drug, that the following case is reported.

CASE REPORT

A 70 year unmarried woman, in general good health but of distinctly psychoneurotic tendencies, presented herself on July 21, 1955, with an extensive ecchymosis of the leg, the result of a slight blow four days before. She was well nourished, weighing 131 pounds. Blood pressure was 125/70 mm. of Hg. There was no evidence of fracture. She was advised to use the limb sparingly, but when she returned to the office on August 15 she still complained of great pain, although most of the

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ecchymosis had disappeared and no lesion was evident. Her symptoms continued unabated, with the added complaints of headache, poor sleep, poor appetite and constipation. Since examination again failed to reveal a sufficient local or systemic lesion to account for her generalized complaints, chlorpromazine (Thorazine), 10 mg. three times a day, was prescribed on September 19. She took the tablets for six days (a total of 180 mg.), without symptomatic benefit, and then discontinued them. She appeared at our office again on October 10, two weeks after having stopped the drug, stating that she had had a chill the previous evening, followed by fever, and that all of her former symptoms remained unabated. We found her to have a temperature of 100° F. We detected no scleral or skin discoloration or other abnormal physical finding, but the urine showed a 2 plus bile discoloration and a 4 plus urobilinogen reaction. The patient was admitted to the hospital the next day (October 11) with a temperature of 101° F., and a pulse rate of 84. On the next day the highest temperature reading was 99.6° F.; thereafter it remained normal. On October 13 scleral jaundice and a labial herpes were first noted. The urine was now deeply bile-stained but showed only a trace of urobilinogen. No urobilinogen was demonstrable after October 18, the urine continuing to be heavily-stained, the skin increasingly so. The picture remained unchanged through this period of hospitalization, which ended on November 9.

During the hospital stay the following blood laboratory data were recorded:

Hemoglobin, 15 gm.; white blood count, 9,900; hematocrit, 45%. There were 8% eosinophils but an otherwise normal cell distribution. Prothrombin, 74%; thymol turbidity, 6 units; cephalin-cholesterol flocculation, negative; alkaline phosphatase, 22 Bodansky units; Kahn (cardiolipin) test, negative; amylase, 86 Somogyi units; urea nitrogen, 9 mg.%; cholesterol, 346 mg.%. The stool was repeatedly negative for occult blood.

The patient was observed at home at weekly intervals. Her chief complaints were pruritus and poor appetite. Jaundice remained intense; repeated urinalysis showed heavy bile content but no trace of urobilinogen. The patient was re-admitted to the hospital on December 17 and an exploratory operation was done by Dr. Gerhard Gruenfeld on December 20, 1955. No stones or obstruction was found in the biliary system by palpation. Forty cubic centimeters of Urochon injected into the empty gall-bladder gave a cholangiogram showing no evidence of stone or obstruction in the common duct. The Urochon entered the duodenum and went well into at least one of the hepatic ducts. A small knife liver biopsy was taken. The patient left the operating table in good condition. On the day preceding operation the following laboratory data were recorded: blood total protein, 5.1 gm.%; albumin, 3.5 gm.%; globulin, 1.6 gm.%; alkaline phosphatase, 8.1 Bodansky units; icterus index, 75 units.

Sections of the liver biopsy * showed a relatively well preserved lobular pattern. While there was a slight increase in periportal fibrous tissue, there was no evidence of periportal inflammation. Furthermore, the bile ducts appeared clear. Hepatic cells also showed no significant alteration. The pathologic findings were limited to the bile canaliculi, which were dilated and filled with inspissated bile. In many areas they formed tiny concretions. This process involved every lobule in the sections, and was generally most intense about the central veins (figure 1).

The patient made a rapid postoperative recovery and left the hospital with the clinical status unaltered. On weekly home observation the jaundice remained intense, and urobilinogen was constantly absent from the heavily bile-stained urine. The only therapy was a limitation of fat in the diet, occasional intramuscular injection of vitamin K, and various sedatives. On February 1, 1956, urobilinogen, 3 plus, appeared in the urine for the first time, although the urine remained heavily bile-stained. Urobilinogen continued in great excess for the next four weeks, with

* Pathology report by Herman T. Blumenthal, M.D.

gradual diminution of the bile content. On March 16 a diminishing skin and scleral jaundice, an absence of urine bile and a urobilinogen of 1 plus were noted. The weight was 101 pounds, a loss of 21 pounds since the onset of jaundice. The urine has subsequently remained free of bile and of excess urobilinogen. The skin discoloration faded very gradually, and there has been a gradual gain in weight.

FIG. 1. Section of liver biopsy. Hematoxylin-eosin stain, magnification approximately 200 ×. Arrows indicate plugs of bile in biliary canaliculi in the region of a central vein. Hepatic cells appear to be normal.

SUMMARY

A case is reported of about 150 days of jaundice of the intrahepatic obstructive type. During 100 days of this period the jaundice was total, no bile entering the intestine. The jaundice followed the administration of only 180 mg. of chlorpromazine during a six-day period. The clinical picture of obstructive jaundice, together with the liver biopsy, was typical of what has been described in other cases of chlorpromazine sensitivity.

SUMMARIO IN INTERLINGUA

Un femina de 70 annos de etate, qui se trovava in un generalmente bon stato de sanitate, disveloppava—post trauma de minor severitate—multiple gravamines neurotic. Esseva prescribite pro illa chlorpromazina (Thorazina), in doses de 10 mg tres vices per die. Le femina prendeva le medicina durante sex dies (= 180 mg). Duo septimanas post le ultime dose illa disveloppava basse grados de febre e bile in le urina. Le febre dispareva intra alicun dies, sed le patiente deveniva profundemente

jalnessate. Le constatationes laboratorial esseva illos de jalnessa obstructive. Post 77 dies, un operation exploratori esseva effectuate que revelava nulle signo de un obstruction extrahepatic. Le biopsia hepatic monstrava normal cellulas hepatic sed dilatate canaliculos biliari que contineva bile de forma inspissate. In le curso del tempore le patiente se restabliva satisfactorimente, sed le bile non dispareva completemente ab le urina durante un periodo de 150 dies.

Ni basse dosages ni breve periodos del administration de chlorpromazina es un garantia contra le occurrentia de prolongate e gravemente disquietante jalnessa.

BIBLIOGRAPHY

1. Isaacs, B., Macarthur, J. G., and Taylor, R. M.: Jaundice in relation to chlorpromazine therapy, Brit. M. J. 2: 1122–1124 (Nov. 5) 1955.

CONSTITUTIONAL HEPATIC DYSFUNCTION * †

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Introduction

Jaundice is ordinarily considered to be a sign of altered bilirubin metabolism. The significance of this symptom is evident when one considers the elaborate studies carried out in an attempt to clarify the mechanism in any given case. Occasionally the opportunity arises to study a patient with jaundice who apparently does not fit into any of the standard categories, and in whom the presence of an elevated bilirubin is compatible with good health.

Constitutional hepatic dysfunction was probably first described by Gilbert and his associates in 1902. Since that time, several excellent reviews of this subject have been presented, and the reader is referred to the accompanying bibliography for details of the historical development of the diagnostic features of this syndrome.[1–8] The error of metabolism lies in the inability of the hepatic cell to process bilirubin at a normal rate. The patients demonstrate a variable degree of icterus with normal liver function studies, and show no evidence of a hemolytic process or obstruction to the intrahepatic or extrahepatic biliary passages. There is no hereditary tendency in any of the reported material available on this subject. As can be seen from the above, the diagnosis is somewhat that of exclusion of the usual causes of jaundice. However, the diagnosis can be more firmly established through the use of a liver biopsy, as was done on this patient.

Case Report

A 22 year old white male medical student was admitted to the University Hospital with a chief complaint of scleral icterus. He was asymptomatic, but two days

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TABLE 1

	11/20/53	11/25/53	1/10/54	11/30/54	3/8/55
van den Bergh					
Direct	0.6	0.7	0.6	0.9	1.1
Indirect	3.4	2.3	3.2	1.6	3.2
Cholesterol	104			145	123
% Esters	73%			78%	77%
Prothrombin	70		70	120	
Thymol	Neg.		Neg.	Neg.	Neg.
Cephalin	Neg.		Neg.	Neg.	Neg.
Alkaline phosphatase	4.7				
BSP				5	

	1/11/54	1/12/54
24 hour urine urobilinogen	7.5 mg.	11.2 mg.

before admission he had noticed that his sclerae appeared yellow. A van den Bergh was found to be abnormally elevated and he was hospitalized with a tentative diagnosis of infectious hepatitis. He had noted no untoward symptoms—this was purely an incidental observation. Past history was not remarkable except that several years before admission, while he was working in a laboratory, a blood sample had been

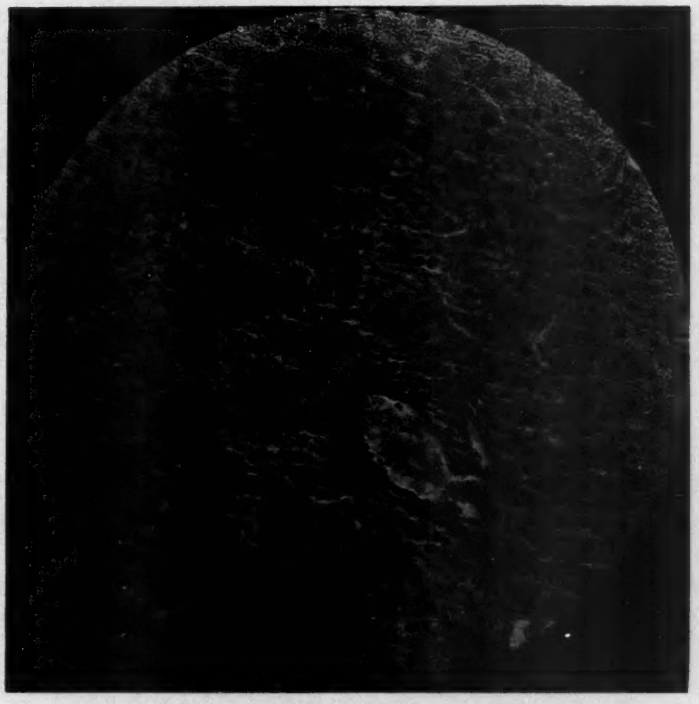

FIG. 1. Needle biopsy of liver showing normal liver structure.

obtained from him which showed that there was a significant degree of icterus in the supernatant plasma at that time. However, this was attributed to hemolysis occurring after the blood had been drawn, and no further investigation was carried out. There was no history of jaundice in the family; the parents and two siblings were carefully checked for the presence of jaundice and none was found.

Physical examination revealed a blood pressure of 130/80 mm. of Hg and normal vital signs. The patient was well developed and well nourished and in no distress. The sclerae were mildly icteric and the skin was clear. A careful abdominal examination failed to reveal evidence of enlargement of either the liver or the spleen. There was no significant adenopathy. The remainder of the physical examination was essentially normal.

Laboratory data are summarized in table 1. During the first admission to the hospital the patient was carefully studied by the Hematology Service (Dr. B. K. Wiseman) and no evidence of a hemolytic process was discovered. Urobilinogen excretions were within normal limits. It will be noted that all of the liver function studies remained within normal limits. The patient was tentatively diagnosed as having infectious hepatitis, and was treated with a prolonged course of bed-rest. In spite of this, a mild degree of jaundice persisted. A few months later he was readmitted to the University Hospital and at this time a punch biopsy of the liver was carried out. Photograph of a representative section of the biopsy is shown in figure 1. This was interpreted as normal liver. At this time a diagnosis of constitutional hepatic dysfunction was considered to have been established, and the patient resumed his normal activities as a medical student. Since his discharge from the hospital his activities have been normal, and he has noted no unusual symptoms indicating any degree of hepatic dysfunction. There has been a persistence of the mild icterus, as will be noted in table 1.

Discussion

We feel that this case illustrates the pitfalls of the diagnosis of this disease, as well as the importance of its early recognition. As far as can be determined, there are no late sequelae to the disease, and no treatment is indicated.[7, 8] However, its consideration in the differential diagnosis of jaundice and its prompt recognition will prevent prolonged and costly studies to exclude a serious metabolic disease. There is no evidence that this condition in any way excludes an individual from consideration for any job or activity.

Summary and Conclusion

1. A case of constitutional hepatic dysfunction is presented.

2. The importance of the consideration of this condition in the differential diagnosis of mild degrees of jaundice is discussed.

Summario in Interlingua

Dysfunction hepatic constitutional es definite como un condition in que le patiente demonstra variabile grados de ictero in le absentia de omne anormalitate del function hepatic, de omne signo de un processo hemolytic, e de omne indice de obstruction intra- o extrahepatic del vias biliari.

Es reportate un caso. Le pertinente aspectos diagnostic del morbo es passate in revista. Es sublineate le importantia de prender iste condition in consideration

in le diagnose differential de jalnessa in patientes in qui le tests ordinari del function hepatic es normal. Es includite un breve revista del litteratura relative a iste condition.

BIBLIOGRAPHY

1. Schiff, L.: Serum bilirubin in health and disease, Arch. Int. Med. **40**: 800, 1927.
2. Rozendaal, H. M., Comfort, M. W., and Snell, A. M.: Slight and latent jaundice; the significance of elevated concentration of bilirubin giving an indirect van den Bergh reaction, J. A. M. A. **104**: 374 (Feb. 2) 1935.
3. Comfort, M. W.: Constitutional hepatic dysfunction, Proc. Staff Meet., Mayo Clin. **10**: 57, 1935.
4. Malloy, H. T., and Lowenstein, L.: Hereditary jaundice in the rat, Canad. M. A. J. **42**: 122–125 (Feb.) 1940.
5. Dameshek, W., and Singer, K.: Familial non hemolytic jaundice; constitutional hepatic dysfunction with indirect van den Bergh reaction, Arch. Int. Med. **67**: 259 (Feb.) 1941.
6. Curry, J. J., Greenwalt, T. J., and Tat, R. J.: Familial non hemolytic jaundice. Report of a case with liver biopsy, New England J. Med. **226**: 909, 1942.
7. Comfort, M. W., and Hoyne, R. M.: Constitutional hepatic dysfunction: clinical study of thirty-five cases, Gastroenterology **3**: 155–163 (Sept.) 1944.
8. Comfort, M. W.: Constitutional hepatic dysfunction, M. Clin. North America **29**: 982 (July 29) 1945.

ERRATUM

In the article by S. D. Pomrinse, M.D., entitled "The Role of the Internist in Restorative Services for the Aged," which appeared in the November, 1957, issue of the ANNALS OF INTERNAL MEDICINE, the following correction should be made on page 900, lines 28 and 29: For the statement, "'. . . there are some 10 million with diabetes. . . .' substitute, 'there are over two million with diabetes. . . .'"

EDITORIAL

ERYTHROPOIETIN

RECENT studies from a variety of sources would seem to establish the existence of a humoral substance capable of stimulating erythropoiesis and, under certain experimental conditions, even producing a polycythemic state. In contradistinction to certain essential metabolites such as iron, folic acid, and cyanocobalamin which may be looked upon as necessary building blocks for erythrocyte maturation, the plasma erythropoietic stimulating factor seems to be fundamentally concerned in the regulatory mechanism which maintains the remarkable constancy of the red cell mass in health, which stimulates erythropoiesis after hemorrhage or after exposure to an atmosphere of reduced oxygen tension, which inhibits the production of red blood cells after hyper-transfusion, and which produces the polycythemia associated with the administration of cobalt.

In 1906, Carnot and Deflandre [1] reported that the injection of plasma of anemic rabbits produced a rise in the red cell count of normal rabbits. These investigators labelled the hypothetical component of anemic plasma, hemopoietine, and suggested that the erythropoietic stimulus of anoxia was mediated by this factor. Repeated attempts in succeeding years either failed to confirm this observation or produced unconvincing results. In 1948, Bonsdorff and Jalavista [2] revived the humoral theory and suggested the term, erythropoietin, for the plasma factor.

The importance of the oxygen content of arterial blood in the regulation of erythropoiesis has been recognized for many years.[3] Reduction in the oxygen tension of inspired air, hypoxic anoxia, whether occurring naturally in individuals living at high altitudes, or in the laboratory under experimental conditions simulating high altitude, regularly produces evidences of increased erythropoiesis. Similar phenomena are, of course, well known in hypoxic hypoxia resulting from congenital malformations of the heart and great vessels as well as in chronic pulmonary disease. Reduction in tissue oxygen tension may also result from a diminution of the hemoglobin level or red cell count. This phenomenon is referred to as anemic anoxia.

Hurtado and others [4] documented the reciprocal relationship between arterial oxygen saturation and erythrocyte values in Andean natives living at high altitude. Such individuals living at an altitude of 14,900 feet showed average red cell counts of 6.15 million, hemoglobin content of 20.8 gm., and

[1] Carnot, P., and Deflandre, C.: Sur l'activité hemopoietique du serum, Compt. rend. Acad. d. sc. **143**: 384, 1906.

[2] Bonsdorff, E., and Jalavista, E.: On the humoral mechanism in anoxic erythrocytosis, Acta physiol. Scandinav. **16**: 150, 1948.

[3] Grant, W. C., and Root, W. S.: Fundamental stimulus for erythropoiesis, Physiol. Rev. **32**: 449, 1952.

[4] Hurtado, A., Merino, C., and Delgado, E.: Influence of anoxemia on the hemopoietic activity, Arch. Int. Med. **75**: 284, 1945.

an average hematocrit of 60. Other investigators have demonstrated a significant erythroid hyperplasia in the bone marrow as well as reticulocytosis in the circulating blood. It is of interest to note that at an altitude of 20,000 feet, with oxygen saturation of only 60–70%, the hemoglobin concentration of the erythrocytes is lowered indicating that increasing anoxia ultimately interferes with hemoglobin production. It is also noteworthy that when individuals living at high altitudes are brought down to sea level a gradual regression of red cell values to normal occurs. During this process diminution of erythropoiesis can be demonstrated.

The converse of the above situation has been observed in experimental studies in which the tissue oxygen tension has been increased. Birkhill et al.[5] demonstrated that when the circulating red cell mass was increased 40% by transfusions there was almost a complete cessation of red cell production. Tinsley et al.[6] exposed patients with hemolytic anemia showing marked reticulocytosis to atmospheres of 50–70% oxygen and observed a regular decrease in reticulocytes.

Observations such as those cited above led by inference to the widely held belief that the oxygen tension of the bone marrow was the primary regulating factor in erythropoiesis. This hypothesis was challenged by direct measurement of the oxygen tension and saturation of the bone marrow in a variety of experimental situations. Grant and Root[7] made such measurements in dogs which had been bled to 30% of their blood volume over a period of three days and found no decrease in oxygen tension or saturation. In a further study Grant[8] maintained dogs in a moderately anemic state by frequent small bleedings over a period of 100 days and again failed to demonstrate bone marrow anoxia. Berk et al.[9] studied the oxygen tension of the marrow in human subjects with chronic anemia or polycythemia vera and found it to be normal. In vitro studies of bone marrow tissue culture revealed that low oxygen tension causes an arrest in erythropoiesis.[10] Thomas[11] found that anoxia arrested heme synthesis by erythroid cells in tissue culture. He could find no level of oxygen tension which would stimulate heme synthesis.

Studies such as those cited above revived interest in the hypothesis that lowered oxygen tension stimulated erythropoiesis through an intermediate

[5] Birkhill, F. R., Maloney, M. A., and Levenson, S. M.: Effect of transfusion polycythemia upon bone marrow activity and erythrocyte survival in man, Blood **6**: 1021, 1951.

[6] Tinsley, J. C., Moore, C. V., Dubach, R., Minnich, V., and Grinstein, M.: The role of oxygen in the regulation of erythropoiesis, J. Clin. Investigation **28**: 1544, 1949.

[7] Grant, W. C., and Root, W. S.: The relation of oxygen in bone marrow blood to posthemorrhagic erythropoiesis, Am. J. Physiol. **150**: 618, 1947.

[8] Grant, W. C.: Oxygen saturation in bone marrow, and in arterial and venous blood during prolonged hemorrhagic erythropoiesis, Am. J. Physiol. **153**: 521, 1948.

[9] Berk, L., Burchenal, J. H., Wood, T., and Castle, W. B.: Oxygen saturation of sternal marrow blood with special reference to pathogenesis of polycythemia vera, Proc. Soc. Exper. Biol. and Med. **69**: 316, 1948.

[10] Rosin, A., and Rachmilewitz, M.: Studies on bone marrow in vitro. III. The effect of anoxia and hyperoxia on explanted bone marrow, Blood **3**: 165, 1948.

[11] Thomas, E. D.: In vitro studies of erythropoiesis. II. The effect of anoxia on heme synthesis, Blood **10**: 612, 1955.

factor. Reissman,[12] in 1950, prepared parabiotic pairs of rats which were placed in a special chamber for five weeks during which time one member of the pair breathed normal air while the other breathed an atmosphere composed of 8% oxygen and nitrogen. The arterial oxygen saturation of the former was normal, 97%, while in the latter it was 63%. Both animals were found to have erythroid hyperplasia of the bone marrow. Grant[13] demonstrated the presence of a humoral erythropoietic factor in the milk of lactating mice and rats exposed to intermittent anoxia in a low pressure chamber. Mothers were placed in the low pressure chamber for six hours a day over a period of 10–25 days. Their litters were kept at sea level pressure. At the end of the study period the babies nursed by the intermittently anoxic mothers displayed an increased concentration of hemoglobin and elevation of hematocrit when compared with babies nursed by control mothers maintained at sea level pressure.

Erslev[14] postulated that previous failures to confirm the observations of Carnot and Deflandre might have been due to the inadequate quantities of anemic plasma used and therefore essentially repeated these experiments using larger amounts. Fifty milliliters of anemic rabbit plasma were injected into normal rabbits intravenously on four successive days. A significant rise in reticulocytes, red cell count, and hematocrit occurred. When similar amounts of normal plasma were given no erythropoietic stimulation was noted. Gray and Erslev[15] gave normal rabbits similar amounts of serum of hypoxic rabbits and again noted a significant reticulocytosis. Further studies[16] revealed that maximal erythropoietic activity of either anemic anoxic plasma or hypoxic anoxic plasma occurred in samples obtained 20 or more hours after the establishment of the anoxic state. Maintenance of the anoxic state for 48 hours or more did not increase the activity of the material. Samples obtained three hours after termination of the anemic state revealed only minimal erythropoietic activity.

For many years it has been known that the administration of cobalt far in excess of normal dietary requirement results in the production of polycythemia in many animal species.[17] That this is due to increased erythropoietic activity is evidenced by the concurrent erythroid hyperplasia of the bone marrow and peripheral reticulocytosis. Since the cobaltous ion is known to have a marked inhibitory action, in vitro, on the endogenous respiration of a number of tissues it was assumed that its mode of action

[12] Reissman, K. R.: Studies on the mechanism of erythropoietic stimulation in parabiotic rats during hypoxia, Blood **5**: 372, 1950.

[13] Grant, W. C.: The influence of anoxia of lactating rats on blood of their normal offspring, Blood **10**: 334, 1955.

[14] Erslev, A. J.: Humoral regulation of red cell production, Blood **8**: 349, 1953.

[15] Gray, D. F., and Erslev, A. J.: Reticulocytosis induced by serum from hypoxic animals, Proc. Soc. Exper. Biol. and Med. **94**: 283, 1957.

[16] Erslev, A. J.: Observations on the nature of the erythropoietic serum factor. II. Erythropoietic activity of serum and bone marrow after time limited exposure to anemic and hypoxic anoxia, J. Lab. and Clin. Med. **50**: 543, 1957.

[17] Schultze, M.D.: Metallic elements and blood formation, Physiol. Rev. **20**: 37, 1940.

was through inhibition of those enzymatic activities which deal with the transport of oxygen and that the resulting tissue anoxia produces polycythemia. Laforet and Thomas [18] found that cobalt inhibited heme synthesis in bone marrow cultures in vitro suggesting that a direct tissue anoxia was probably not the mechanism of cobalt action. In recent studies Goldwasser et al.[19] reported the presence of an increased amount of erythropoietin in the plasma of rats ten hours after the injection of cobaltous chloride. Injection of this "cobalt plasma" into starved rats stimulated the incorporation of Fe^{59} into the red cells in a manner quantitatively equivalent to anemic plasma. Although additional studies will be essential to establish the point, these observations strongly suggest that the action of cobalt, like anemia and hypoxia, lies in the production of an increased amount of plasma erythropoietin.

Physiologic studies indicate that the plasma erythropoietic stimulating factor produces erythroblastic multiplication rather than a speeding up of maturation. The usual observed sequence of events is a significant increase in the number of circulating reticulocytes two or three days after the application of the stimulus followed in several more days by a rise in the red cell count. Plzak et al.[20] have used Fe^{59} to measure erythropoietic activity. Fe^{59} is injected two to five hours after the last of a series of injections of the plasma under study. Within 4–6 hours after injection the Fe^{59} has been removed from the circulating plasma. The proportion of radioactive iron reappearing in red cells at 12 hours is considered a measure of the rate of erythropoiesis since Fe^{59} is known to be incorporated into maturing red cells. Anemic rat plasma was found to stimulate a two-fold increase in the iron uptake of normal rats as compared to saline injected controls. In subsequent experiments [21] hypophysectomized rats were found to be more sensitive test objects. In such animals there is a ten-fold decrease in erythropoietic activity and the injection of anemic plasma produces a three- to seven-fold increase in Fe^{59} uptake. As the result of a series of experiments employing rats made polycythemic by the intraperitoneal injection of homologous erythrocytes, rats maintained in an atmosphere of 85–95% oxygen, starved rats, and rats previously treated with dinitrophenol, Fried et al.[22] suggested that the rate of erythropoiesis is regulated not so much by the absolute oxygen tension of the blood as by the relationship between oxygen tension and the oxygen demand of the tissues.

[18] Laforet, M. T., and Thomas, E. D.: The effect of cobalt on heme synthesis by bone marrow in vitro, J. Biol. Chem. **218**: 595, 1956.

[19] Goldwasser, E., Jacobson, L. O., Fried, W., and Plzak, L.: Mechanism of the erythropoietic effect of cobalt, Science **125**: 1085, 1957.

[20] Plzak, L., Fried, W., Jacobson, L. O., and Bethard, W. F.: Demonstration of stimulation of erythropoiesis by plasma from anemic rats using Fe^{59}, J. Lab. and Clin. Med. **46**: 671, 1955.

[21] Jacobson, L. O., Plzak, L., Fried, W., and Goldwasser, E.: Plasma factor(s) influencing red cell production, Nature **177**: 1240, 1956.

[22] Fried, W., Plzak, L., Jacobson, L. O., and Goldwasser, E.: Studies on erythropoiesis. III. Factors controlling erythropoietin production, Proc. Soc. Exper. Biol. and Med. **94**: 237, 1957.

The source of plasma erythropoietin is still not clear. A considerable body of work deals with the possibility of an endocrine origin. Van Dyke et al.[23] critically reviewed the evidence for involvement of the thyroid, gonads, adrenals, and pituitary in erythropoiesis and concluded that, with the exception of the anterior pituitary, the other endocrine organs could not be implicated in the fundamental control of erythropoiesis. These investigators [24] were able to prepare an anterior pituitary extract free of all other trophic hormones with which they were able to demonstrate repair of the anemia of hypophysectomized rats and even to produce polycythemia in normal animals. Other investigations [21, 22] have shown that the hypophysectomized animal is, however, still capable of producing increased amounts of plasma erythropoietin following bleeding, in response to hypoxic hypoxia, as well as after the administration of cobalt. A pituitary source of erythropoietin would thus seem to be excluded. Van Dyke et al. raise the question of the possible existence of two plasma erythropoietic stimulating factors, one of anterior pituitary origin, the other from some as yet unknown source. Jacobson et al.[25] recently reported a series of experiments in which separate removal of the adrenals, pituitary, thyroid, spleen, gonads, pancreas, stomach, intestines, and a major portion of the liver, did not impair the ability to produce erythropoietin under the stimulus of bleeding or cobalt administration. Only when the kidneys were removed was there an apparent failure to produce erythropoietin after the appropriate stimulus. Mirand and Prentice [26] were not able to confirm this observation. The question remains *sub judice*. Erslev and Lavietes [27] treated rabbits with HN_2 prior to bleeding and were still able to demonstrate the presence of erythropoietin in the plasma. Linman and Bethell [28] reported that rabbits subjected to total body irradiation were still able to produce erythropoietin. These experiments would appear to rule out the lymphatic and hemopoietic tissues as sources of erythropoietin.

The chemical nature of erythropoietin has not yet been determined. Borsook et al.[29] found it to be present in the protein-free filtrate of boiled, acidified plasma. Other investigators have confirmed this finding. Linman and Bethell [28] state that erythropoietin does not appear to be species specific,

[23] Van Dyke, D. C., Contopoulos, A. N., Williams, B. S., Simpson, M. E., Lawrence, J. H., and Evans, H. M.: Hormonal factors influencing erythropoiesis, Acta hematol. 11: 203, 1954.

[24] Van Dyke, D. C., Simpson, M. E., Contopoulos, A. N., and Evans, H. M.: The separate existence of the pituitary erythropoietic hormone, Blood 12: 539, 1957.

[25] Jacobson, L. O., Goldwasser, E., Fried, W., and Plzak, L.: Role of the kidney in erythropoiesis, Nature 179: 633, 1957.

[26] Mirand, E. A., and Prentice, T. C.: Presence of plasma erythropoietin in hypoxic rats with and without kidney(s) and/or spleen, Proc. Soc. Exper. Biol. and Med. 96: 49, 1957.

[27] Erslev, A. J., and Lavietes, P. H.: Observations on the nature of the erythropoietic serum factor, Blood 9: 1055, 1954.

[28] Linman, J. W., and Bethell, F. H.: The effect of irradiation on the plasma erythropoietic stimulating factor, Blood 12: 123, 1957.

[29] Borsook, H., Graybiel, A., Keighly, G., and Windsor, E.: Polycythemic response in normal adult rats to a non-protein plasma extract from anemic rabbits, Blood 9: 734, 1954.

nor is it antigenic. Extracts which were ashed were inactive suggesting that it is organic in nature. Using Fe^{59} incorporation into erythrocytes as the assay method, Gurney et al.[30] were able to demonstrate erythropoietin in normal plasma which was concentrated ten times. Erythropoietin has been demonstrated in the urine of anemic individuals.[31]

The clinical implications of all of these studies, which seem to demonstrate beyond any doubt the existence of a plasma erythropoietic stimulating factor, remain, as yet, incompletely explored. Contopoulos et al.[32] using extracts of boiled, acidified plasma of patients with polycythemia vera and stress polycythemia found increased erythropoietin content. These investigators gave 30 mg. of the lyophilized extract per day for fourteen days to hypophysectomized rats and noted a 25% increase in total circulating red cell volume and hemoglobin at the end of the treatment period. Linman and Bethell[33] reported similar findings not only in polycythemia vera, but also in secondary polycythemia. It is still too early to assay the significance of these intriguing findings. Several groups of investigators have found elevation of erythropoietin content in the plasma of patients with a variety of anemias. Luhby et al.[34] report evidence of increased erythropoietin activity in the plasma of six of seven patients with Cooley's anemia and one of two patients with sickle cell anemia. The plasma of one patient with hypoplastic anemia was found to be inactive. Gurney et al.[35] treated two patients with congenital hypoplastic anemia with the plasma of anemic human donors of the same blood group. Daily infusions of 300 ml. of anemic plasma for 6–8 days resulted in an increased per cent of reticulocytes never previously seen in these patients. They suggested the possibility of a congenital deficiency of erythropoietin in this disease.

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[30] Gurney, C. W., Goldwasser, E., and Pan, C.: Studies on erythropoiesis. VI. Erythropoietin in human plasma, J. Lab. and Clin. Med. **50**: 534, 1957.

[31] Hodgson, G., and Toha, J.: The erythropoietic effect of urine and plasma of repeatedly bled rabbits, Blood **9**: 299, 1954.

[32] Contopoulos, A. N., Lawrence, J. H., McCombs, R. K., and Simpson, M. E.: Erythropoietic activity in the plasma of polycythemic patients, Clin. Res. Proc. **5**: 30, 1957.

[33] Linman, J. W., and Bethell, F. H.: The plasma erythropoietic stimulating factor in man. Observations on patients with polycythemia vera and secondary polycythemia, J. Lab. and Clin. Med. **49**: 113, 1957.

[34] Luhby, A. L., Piliero, S. J., Medici, P. T., Pansky, B., and Gordon, A. S.: Studies on circulating erythropoietin in anemic human subjects, Clin. Res. Proc. **5**: 89, 1957.

[35] Gurney, C. W., Pierce, M. I., Schrier, S. E., Carson, P. E., and Jacobson, L. O.: The stimulatory effect of "anemic plasma" in congenital hypoplastic anemia, J. Lab. and Clin. Med. **50**: 821, 1957.

REVIEWS

Signs and Symptoms: Applied Pathologic Physiology and Clinical Interpretation. 3rd Ed. Edited by CYRIL MITCHELL MACBRYDE, A.B., M.D., F.A.C.P. 973 pages; 16 × 23.5 cm. J. B. Lippincott Co., Philadelphia. 1957. Price, $12.00.

The third edition of this popular text maintains the excellent standards set previously. The several contributors discuss signs and symptoms of disease in clear, concise style. There is a uniformly high level of authorship, for which the editor deserves commendation. Each section is concerned with normal function, the derangement of this function by various pathologic entities which produce symptoms, and methods for diagnosing pertinent diseases. Psychosomatic factors receive appropriate attention. The focal point of each treatise is the patient, his history and physical findings; therefore emphasis is placed on technics, intellectual as well as biochemical, for analyzing these data so as to arrive at a proper cause for the complaints. To facilitate such an approach, the chapters are constructed about symptoms or abnormal physical findings rather than diseases. Each chapter has a good bibliography and the book is well indexed. All physicians and medical students will find this a useful, instructive book.

JEROME E. COHN, M.D.

Atlas of Clinical Endocrinology. By H. LISSER, A.B., and ROBERTO F. ESCAMILLA, M.D. 476 pages; 22 × 28.5 cm. C. V. Mosby Co., St. Louis. 1957. Price, $18.75.

This recent edition to the medical literature will be limited in its usefulness to those readers who are not concerned with a broader understanding of the human endocrinopathies. The stated purpose of the book is to offer a visual presentation of endocrine disorders with an abbreviated text containing all essentials of adequate diagnosis and therapy including details of dosage. The fundamentals of endocrine physiology, pathology and chemistry are specifically excluded.

The authors have accomplished their stated mission but at a cost detrimental to the value of the book. There are 148 plates, many of which are poorly reproduced. The poor reproductions are usually those photographs which have reappeared so many times in publications dealing with endocrine pathology, that their inclusion in this work can be excused only for historical reasons or a compulsion toward completeness.

The telegraphic style and arbitrary didactics will be annoying to some readers. The authors reveal lack of understanding of some of the more common gynecologic problems such as infertility and the climacteric. Here as in other aspects of endocrine discussions if the therapeutic directions are followed literally, there will be many frustrated and disappointing results of therapeusis. Search of the book failed to reveal any reference to the interesting and not uncommon Chiari-Frommel syndrome.

The inclusion of the *Atlas of Clinical Endocrinology* in a reference library will provide a pictorial aid in the physical diagnosis of most of the human endocrinopathies. The therapeutic usefulness is definitely limited. This is but another example of the great difficulty encountered in the preparation of a complete account of the endocrinopathies which belong to the several medical disciplines.

ARTHUR L. HASKINS, M.D.

Systemic Arterial Embolism: Pathogenesis and Prophylaxis. By JOHN MARTIN ASKEY, M.D. Modern Medical Monographs No. 14. 157 pages; 14.5 × 22.5 cm. Grune & Stratton, New York. 1957. Price, $5.75.

This relatively short monograph is presented in a terse, succinct but eminently readable style. In his preface the author well states that in so controversial a field as that of thromboembolism, many crucial decisions in treatment must be based on presumptive evidence which can only be assessed clinically. It is important then periodically to assemble, analyze and crystallize accrued evidence to date to form a working hypothesis in therapy. This goal Dr. Askey attains with sufficient inclusiveness but always with a pleasant conciseness. The author divides each of his nine chapters into consideration of rheumatic, followed by that of arteriosclerotic heart disease and in the latter, of course, acute coronary thrombosis figures prominently. All facets of recent thought on cardiac clot formation and mobilization are well covered and, where pertinent, the author rightly adds his personal beliefs and conclusions. This latter applies especially to the two final chapters dealing solely with "Prophylactic Antithrombotic Measures." While adequately covering other therapeutic weapons, discussion here is largely that of anticoagulant therapy. In the therapeutic field the author in no instance straddles any of the so-called "controversial" issues. He agrees with widespread favorable statistics culminating in the dictum of the International Conference on Thrombosis and Embolism at Basel: "Anticoagulant drugs should be given to every patient with acute myocardial infarction unless there are contraindications." At this point and as regards the accepted beneficial effects of anticoagulants in acute myocardial infarction a note of regret is interjected. For many years, even prior to anticoagulant therapy, a great host of autopsy and other statistics stressed the importance of *peripheral* (venous) thromboembolic lesions in this disease. Thus, Wright in his monograph declares these (peripheral) lesions "in some cases produce more serious consequences than do the original coronary occlusions." The value of anticoagulant prophylaxis against such peripheral lesions cannot be ignored, yet one finds in the book little or no mention of this aspect. While Dr. Askey may have felt he must stick strictly to his last (systemic *arterial* embolism) this reader had a slightly awkward sense of incompleteness.

The author definitely agrees with the increasing number of experienced anticoagulant therapists who deny the therapeutic division of acute coronary cases into so-called "good and bad risk" cases. The essential premise that anticoagulants cause "as much mortality as is found in 'good risk' patients" is today untenable. Other refutations are included in the text. The author naturally approves the accepted continuous (long-term) anticoagulant therapy to certain patients with mitral stenosis and systemic embolism who are ineligible for mitral valvuloplasty. Likewise he joins those advocating continuous therapy to "patients surviving a severe or recurrent myocardial infarction." The statement that anticoagulant therapy is indicated on the appearance of congestive failure in rheumatic and arteriosclerotic heart disease is bolstered by rational statistics. Despite this one wonders if the present therapeutic hesitancy by many clinicians will change.

In the early days of anticoagulant therapy the adequate prophylaxis obtained by a "conservative" depression of prothrombin (50 to 40%) was frowned on by all, with but a few notable exceptions. Dr. Askey notes the modern trend to more conservative depressions and cites his own belief that "in ambulatory patients a reduction in prothrombin activity to 50% is satisfactory."

It is notable that, despite the brevity of this monograph, something of an innovation is introduced in appending a "summary" at the end of each chapter. Because of this and the terse inclusiveness of the book as a whole, the average interested

clinician can read it with pleasure and profit. The anticoagulant therapist will read it and want to keep it close at hand.

H. Raymond Peters, M.D.

Modern Therapy in Neurology. Edited by Francis M. Forster, M.D. 792 pages; 14.5 × 22.5 cm. C. V. Mosby Company, St. Louis. 1957. Price, $12.00.

This volume, which presents the current status of therapy of nervous system diseases, was edited with the assistance of 15 contributors. There are 792 pages and 18 chapters, each dealing with a major group of neurological diseases. The emphasis is almost entirely on treatment, although there are a few paragraphs on diagnosis or pathophysiology of some disease entities. These paragraphs appear more to support the rationale of certain treatments than to serve as an aid in diagnosis. Each chapter is preceded by an outline of its contents which, in conjunction with heavier print to designate the sections of each chapter, make this book useful as a rapid reference volume. Most chapters are followed by a complete bibliography of the pertinent literature. This book is a most desirable addition to the medical literature and fulfills a need which has become quite apparent over the past few years. It is a volume which will be useful to all practitioners of medicine.

C. V. B.

A Manual of the Common Contagious Diseases. 5th Ed. By Philip Moen Stimson, A.B., M.D., and Horace Louis Hodes, A.B., M.D. 624 pages; 13.5 × 20 cm. Lea & Febiger, Philadelphia. 1956. Price, $8.50.

Some years ago when the reviewer was an intern just entering an infectious disease service, an earlier edition of this book was among those recommended to him for orientation into the common contagious diseases. It served this purpose well. This new edition, revised and expanded to include up-to-date information, especially on pathogenesis and treatment, would also seem to serve as a very good practical guide to medical students, house officers, practicing physicians and nurses. The title gives a clue to the relatively restricted selection of subject matter; only diphtheria, Vincent's angina, streptococcal infection, measles, rubella, whooping cough, mumps, chickenpox, smallpox, acute bacterial meningitis and poliomyelitis are discussed. No mention is made of the common communicable respiratory diseases or enteric diseases. However, each disease considered is discussed in a fairly comprehensive manner.

The introductory chapters vary considerably in quality, particularly in consideration of basic concepts. For example, the chapter on principles of contagion, apparently in an attempt to achieve simplicity, is not particularly helpful. On the other hand, the chapter on antibiotics and sulfonamides presents a reasonable general discussion on the practical use of these chemotherapeutic agents even though the section on mode of action might either be expanded or eliminated entirely. On the whole, however, consideration of the individual diseases is good. Important clinical details are given. Considerable emphasis has been properly placed on streptococcal disease and its complications. The text could be shortened somewhat by the elimination of repetitious material. And, as always, there is room for differences of opinion on controversial subjects. Undoubtedly some authorities would not concur with the authors' recommendations on the generous use of prophylactic antibiotics.

The final chapter, General Management of Contagious Diseases, is an important one. Here are preserved detailed instructions for the medical aseptic technic which formerly constituted an integral part of every physician's training but which now is so commonly neglected. From the broad point of view, the book may be recommended as a good practical guide.

Charles L. Wisseman, Jr., M.D.

Radium Therapy: Its Physical Aspects and Extensions with Radioactive Isotopes. By C. W. WILSON, M.Sc., Ph.D., F. Inst. P. 286 pages; 15.5 × 24 cm. The Williams & Wilkins Co., Baltimore. 1956. Price, $7.50.

Since the first edition appeared 11 years ago, Wilson's book has been an indispensable book in the library of radiotherapeutic centers where radium is being used. This new edition has added a series of new subjects in the most modern developments in radiotherapy such as: the use of radioisotopes in radiotherapy, telegamma therapy (Cobalt-60, Iridium-192, Cesium-137), and protection.

The radioactive isotopes used in the therapy of cancer are particularly studied. Their properties and applications are explained.

All types of telegamma apparatus in use today are described with devices for beam direction.

This book contains a lot of information for dosimetry of radium and isotopes, telegamma therapy, and protection. A large number of formulas, tables, and graphs make this book a very useful manual for everyday work in a Department of Radiotherapy.

The problems of dosimetry have been given careful attention, and the chapters in radium dosimetry deserve a special recommendation.

It is one of the best books written on radium therapy—easy to read and understand, very useful for well-trained radiotherapists, and excellent for Board students.

FERNANDO G. BLOEDORN, M.D.

BOOKS RECENTLY RECEIVED

Books recently received are acknowledged in the following section. As far as practicable those of special interest will be selected for review later, but it is not possible to discuss all of them.

Atlas Colangiografico: Tecnica de la Colangiografia Operatoria. By DR. PASCUAL MAGALDI. 251 pages; 23.5 × 16 cm. (paper-bound). 1957. Lopez & Etchegoyen, S.R.L., Buenos Aires. Price, m$n 180.

La Balistocardiographie, Ses Bases Physiques ses Applications Cliniques. By G.-R. RAGER; preface by PROFESSEUR C. LIAN. 108 pages; 25.5 × 17 cm. (paper-bound). 1957. Masson et Cie., Paris. Price, 1.200 fr.

Die Bluteiweisskörper des Menschen. By PROF. DR. MED. FERDINAND WUHRMANN and DR. ING. CHEM. CHARLIE WUNDERLY. 499 pages; 25 × 18 cm. 1957. Benno Schwabe & Co., Basel. Price, $13.00.

Body Water in Man: The Acquisition and Maintenance of the Body Fluids. By MAURICE B. STRAUSS, M.D., Professor of Clinical Medicine, Boston University School of Medicine, etc. 286 pages; 22 × 14.5 cm. 1957. Little, Brown and Company, Boston. Price, $7.00.

Cardio-Charting: Universal Method of Recording Heart Auscultation. By ARTHUR BRISKIER, M.D., Senior Clinical Assistant Physician and Cardiologist, Mount Sinai Hospital, New York City, etc. 58 pages; 26 × 19.5 cm. 1957. The Macmillan Company, New York. Price, $6.00.

The Chronically Ill. By JOSEPH FOX, Ph.D. 229 pages; 22.5 × 14.5 cm. 1957. Philosophical Library, Inc., New York. Price, $3.95.

The Clinical Application of Antibiotics. Volume III. *Chloramphenicol and the Tetracyclines.* By M. E. FLOREY, M.D. 393 pages; 25.5 × 16 cm. 1957. Oxford University Press, New York. Price, $17.50.

Électrocardiographie Endocavitaire. By H. LATOUR and P. PUECH. 294 pages; 25.5 × 17 cm. (paper-bound). 1957. Masson et Cie., Paris. Price, 3.200 fr.

Fads and Fallacies in the Name of Science (formerly published under the title *In the Name of Science*). By MARTIN GARDNER. 363 pages; 20.5 × 14 cm. (paper-bound). 1957. Dover Publications, Inc. New York. Price, $1.50.

The Function of the Ureter and Renal Pelvis: Pressure Recordings and Radiographic Studies of the Normal and Diseased Upper Urinary Tract of Man. (From the Institute for Experimental Medical Research, University of Oslo, and Dept. III, Ullevål Hospital, Oslo, Norway. Head: Professor of Surgery Carl Semb, M.D.) By FREDRIK KIIL, M.D., Research Associate, Institute for Experimental Medical Research, University of Oslo, etc. 218 pages; 24.5 × 17 cm. 1957. W. B. Saunders Company, Philadelphia. Price, $7.50.

Hepatitis Frontiers: Henry Ford Hospital International Symposium, Sponsored by the Henry Ford Hospital, Detroit, Michigan, and held at the hospital October 25, 26, 27, 1956. Editors: FRANK W. HARTMAN, M.D., Medical Research Adviser, Director of Professional Services, Office of the Surgeon General U.S.A.F., Washington, D. C., etc.; GERALD A. LOGRIPPO, M.D., Associate in Charge, Division of Microbiology, Department of Laboratories, Henry Ford Hospital; JOHN G. MATEER, M.D., Physician in Chief, Department of Medicine, Henry Ford Hospital; and JAMES BARRON, M.D., Associate Surgeon, Division of General Surgery, Henry Ford Hospital. 595 pages; 24.5 × 16 cm. 1957. Little, Brown and Company, Boston. Price, $12.50.

Integrating the Approaches to Mental Disease: Two Conferences Held Under the Auspices of the Committee on Public Health of The New York Academy of Medicine. Edited by H. D. KRUSE, M.D., Executive Secretary, Committee on Public Health, The New York Academy of Medicine, New York City. 393 pages; 27 × 18 cm. 1957. Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, New York. Price, $10.00.

Introduction to Biostatistics. By HULDAH BANCROFT, Ph.D., Professor of Biostatistics, Tulane University School of Medicine, New Orleans. 210 pages; 24 × 16 cm. 1957. Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, New York. Price, $5.75.

Lecciones de Alergia. By GUIDO RUIZ MORENO. 196 pages; 23 × 16 cm. (paper-bound). 1957. Lopez & Etchegoyen, S.R.L., Buenos Aires. Price, m$n 70.

Maladies-Vedettes: Maladies d'Avenir, Maladies Quotidiennes, Maladies d'Exception. By FRED SIGUIER. 475 pages; 25.5 × 17 cm. (paper-bound). 1957. Masson et Cie., Paris. Price, 3.500 fr.

Manual of Nutrition. 4th Ed. Originally written by DR. MAGNUS PYKE, Ph.D., F.R.I.C. 70 pages; 24.5 × 15.5 cm. 1957. Philosophical Library, New York. Price, $3.50.

Medical Treatment. By KENNETH MACLEAN, M.A., M.D., F.R.C.P., Physician to Guy's Hospital, etc. With chapters on the Tropical Diseases by COL. W. R. M. DREW, C.B.E., F.R.C.P., D.T.M. & H., Consultant Physician, British Middle East Land Forces. 696 pages; 25.5 × 16 cm. 1957. Distributed in the United States and Possessions by Little, Brown and Company, Boston. Price, $9.50.

Las Nefropatias a Traves de la Biopsia Renal por Puncion: Correlacion Anatomopatologica Clinica y Funcional. By VICTOR RAUL MIATELLO. 273 pages; 23 × 16 cm. (paper-bound). 1957. Lopez & Etchegoyen, S.R.L., Buenos Aires. Price, m$n 150.

Neurologia Basica: Semiologia Clinica Propedeutica. By Dr. Gustavo F. Poch. 253 pages; 23 × 16 cm. (paper-bound). 1957. Lopez & Etchegoyen, S.R.L., Buenos Aires. Price, m$n 90.

Old Doc. By O. H. Perry Pepper, M.D. 247 pages; 21 × 14.5 cm. 1957. J. B. Lippincott Company, Philadelphia. Price, $3.75.

The Physiology of Gastric Digestion. Monographs of the Physiological Society, Number 4. By A. H. James, D.M. (Oxon.), M.D. (Toronto), B.Ch., M.R.C.P., Senior Lecturer in Medicine, Welsh National School of Medicine, and Deputy Director of the Medical Unit, Cardiff Royal Infirmary. 192 pages; 22 × 14 cm. 1957. The Williams & Wilkins Company, Baltimore. Price, $7.00.

Stedman's Medical Dictionary of Words Used in Medicine with Their Derivations and Pronunciation Including Dental, Veterinary, Chemical, Botanical, and Other Special Terms; Anatomical Tables of Titles in General Use, the Terms Sanctioned by the Basle Anatomical Convention; The New British Anatomical Nomenclature; Nomina Anatomica, Revised by the Fifth International Nomenclature Congress of Anatomists; Pharmaceutical Preparations Official in the U. S. and British Pharmacopoeias or Contained in the National Formulary; Biographical Sketches of Figures in the History of Medicine. 19th Ed., with etymologic and orthographic rules. Edited by Norman Burke Taylor, V.D., M.D., F.R.S.C., F.R.C.S. (Edin.), F.R.C.P. (Can.), M.R.C.S. (Lon.), University of Western Ontario and formerly of the University of Toronto; in collaboration with Lieut. Col. Allen Ellsworth Taylor, D.S.O., M.D., Classical Editor. 1,656 pages; 25.5 × 17 cm. (leather-bound). 1957. The Williams & Wilkins Company, Baltimore. Price, $12.50.

The Story of Peptic Ulcer. Conceived by Richard D. Tonkin, M.D., F.R.C.P., Westminster Hospital, London; characterised by Raymond Keith Hellier, F.R.S.A. 71 pages; 20.5 × 14 cm. 1957. W. B. Saunders Company, Philadelphia. Price, $2.25.

Ten Million and One: Neurological Disability as a National Problem. Arden House Conference Sponsored by The National Health Council. 102 pages; 21 × 14 cm. 1957. Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, New York. Price, $3.50.

Tratado de Patologia Interna. Tomo II. Enfermedades del Aparato Digestivo, Peritoneo, Higado, Vesicula y Vias Biliares, Pancreas & Sistema Nervioso. By Enrique G. Fongi, Osvaldo Fustinoni and Pedro C. Rospide. 1,212 pages; 27.5 × 18.5 cm. 1957. Lopez & Etchegoyen, S.R.L., Buenos Aires. Price, m$n 650.

The Year Book of Medicine (1957–1958 Year Book Series). Edited by Paul B. Beeson, M.D., Carl Muschenheim, M.D., William B. Castle, M.D., Tinsley R. Harrison, M.D., Franz J. Ingelfinger, M.D., and Philip K. Bondy, M.D. 752 pages; 20 × 13 cm. 1957. The Year Book Publishers, Incorporated, Chicago. Price, $7.50.